Fatigue in Primary Care

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Fatigue in Primary Care
Course, Prognosis and Diagnoses

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It does not matter if you know everything.
The question is: do you practice it?
Yogi Bhajan

Voor David en mijn ouders

Contents

1

Introduction

Fatigue: many question marks

Fatigue is a common phenomenon that covers a wide range of manifestations, from being a normal part of everyday life to being a symptom of serious disease. It has been defined as 'an overwhelming sustained sense of exhaustion and decreased capacity for physical and mental work', with a verbalization of lack of energy and an inability to maintain usual routines as major characteristics (Piper).[1] Although not life-threatening in itself, fatigue was found to be an independent predictor of mortality rates within a period of ten years in elderly people.[2]

Despite it being so common, several authors have pointed out the difficulties and confusion in defining and describing fatigue[1,3], while reports in qualitative studies by patients undergoing chemotherapy or with rheumatoid arthritis show that within individuals, fatigue can be experienced as unusual or unpredictable compared to previous daily fatigue experiences.[4-6] In contrast to tiredness as a temporary phenomenon of daily life generally related to some identifiable form of exertion, fatigue induced by a disease process or treatment is described as chronic, cumulative and rarely dissipated by sleep.[7] These distinguishing characteristics are in line with reports of healthy employed individuals, describing fatigue as an acute, sometimes overwhelming, but temporary state. Besides subjective physical, emotional or mental and behavioral manifestations, they also mentioned objective physical manifestations in posture, eyes and face.[8]

Another feature of fatigue according to the medical and nursing literature is its subjective nature.[7] Although other symptoms such as pain or depressed mood are also invisible, these symptoms may be more specifically expressed or localised. Fatigue can be experienced both physically and mentally and seems to be more nonspecific; in the ICPC international classification system of primary care, it is coded in the 'general' (A) category. The lack of a common scientific language has been mentioned as a major problem in the description of fatigue.[4] Although fatigue is reported by patients and healthy individuals as a depletion or lack of energy[8,9], this has no common counterpart in medicine.

Depending on the definition used, the reported prevalence in the general population ranges widely, with percentages up to 57%.[3,10] At least in the Netherlands, the incidence of fatigue seems to have increased in the last decennia.[11] Towards the worse end of the continuum of severity and duration, fatigue may become a symptom or health problem that interferes with many aspects of daily life[12-14]; in a community study, of all people 63% experienced chronic fatigue, 38% were very often fatigued and 25% reported a large impact.[10] Most of these complaints are not brought to (the first line of) medical

attention: while many patients attending primary care (also) report being fatigued when asked[15] only 6-16% of fatigued people consult their doctor because of fatigue.[10,11]

Fatigue in primary care

From the GP's point of view, fatigue is a commonly presented symptom. The annual incidence as a symptom diagnosis has been estimated at 2%[11], and fatigue constitutes 5% of annual new episodes[16], 7-9% of primary reasons[17,18] and 19% of secondary reasons for consultation in one month.[17] Patients who present with fatigue may have various reasons to do so: they may experience severe limitations and are often worried about their symptom.[19,20]

Apart from its high prevalence, fatigue is a complex symptom in health care. Although people may look tired, the experience in itself cannot directly be observed, only communicated. For the physician, fatigue is highly nonspecific: a wide range of possible causes may underlie this frequently presented symptom. This means that much information may be needed to find an explanation, including an assessment of whether fatigue is a sign of serious pathology that demands (immediate) intervention by the GP. Fatigue is often accompanied by other symptoms.[10,11] However, co-occurring symptoms are often also nonspecific, such as pain. The co-occurrence of pain and fatigue has been studied in several patient populations with specific (syndrome) diagnoses, but despite the common prevalence rarely in patients consulting with fatigue in primary care. This is important however, since experiencing multiple symptoms may increase limitations in functioning[10,21] and fatigue and pain may share a common aetiology.[22-24]

GPs are the generalists of health care, dealing with a wide range of problems and in the Netherlands also functioning as the gatekeeper to more specialised health care. Whether indications of pathology are present or not, the role of the GP is to diagnose the severity and impact of the problem and accordingly determine adequate management. With little time available and the lack of a clear aetiology, fatigue is often a challenge in this regard, with no straightforward strategy to follow. At present, an official guideline for practical management of fatigue in primary care does not exist in the Netherlands. GPs often perform diagnostic tests[16], while the Dutch guideline for diagnostic testing in patients with 'vague' or unexplained symptoms (1994) recommends to wait and see for one month when history taking and physical examination do not result in a clear conclusion regarding the medical background of the symptom.[25] Recommendations have been formulated for diagnosis and management of patients with chronic, somatically unexplained fatigue.[26] These are however aimed at patients with the chronic fatigue syndrome (CFS) rather than the wider range of patients consulting with fatigue in primary care.

Lack of evidence on prognosis and diagnoses

Similarly, research on fatigue has mainly focused on the CFS. Little high quality evidence exists for the course and prognostic indicators of fatigue in primary care populations. GPs know that fatigue has not resolved in those patients who repeatedly consult for fatigue. However, since the majority of patients do not visit again[11], the course of this frequently presented symptom remains unclear in many cases. Moreover, little information is available on important factors that may predict an either positive or negative outcome.

Likewise, most studies have been performed in populations with 'unexplained' fatigue, which means that patients who received a specific diagnosis were excluded from the study. Therefore, there is little information on the range of diagnostic outcomes based on large primary care populations of patients presenting with fatigue. Similarly, knowledge on the (temporal) co-occurrence of fatigue and other symptoms such as pain in patients visiting the GP is scarce.

Given the high prevalence of this challenging symptom and the many gaps in knowledge, more information is needed on its course and prognosis, on diagnoses recorded by GPs and on the relationship with common co-occurring symptoms in the wide range of patients who present with fatigue. This may help to support adequate management for this large group of patients in primary care.

Objectives and outline of the thesis

We performed a large observational study in primary care in order to enlarge the knowledge base for optimising management of fatigue and provide recommendations for further (intervention) research. Therefore, we included patients presenting with a new episode of fatigue, and followed participants for one year after consulting the GP. We aimed to answer the following research questions:

(1) Which diagnoses that are likely to be associated with fatigue are recorded in the year following the first consultation for fatigue in primary care? We answered this question by performing a descriptive analysis of diagnoses recorded by GPs (Chapter 2).

(2) What is the course of both fatigue, presented as a main symptom in primary care, and functional outcomes? We addressed this question by conducting a systematic overview of the literature (Chapter 3). Subsequently we studied the course of fatigue and associated symptoms and functioning during one year after presentation in our study cohort (Chapter 4).

(3) Which factors predict the course of fatigue? This question was addressed both in the systematic review (Chapter 3) and in the cohort study. We investigated the contribution of a wide variety of potentially prognostic factors, measured in a baseline patient questionnaire, to both a favourable and an unfavourable course, using combinations of repeated measurements of fatigue severity as outcome measure (Chapter 5).

(4) What is the longitudinal relation between fatigue and pain? Given the strong association of pain and fatigue over time in groups of patients with different patterns of fatigue (Chapter 4), and the prognostic value of co-existing pain in fatigued patients (Chapter 5), we decided to study the temporal associations between pain and fatigue using different models assuming either a direct relationship between the symptoms, or a temporal association where a change in one symptom is followed by a change in the other (Chapter 6).

In the general discussion, the results of this study are linked together and put in a wider perspective, concluding with implications for practice and future research (Chapter 7). Finally, the thesis concludes with summaries of the design and results of the research in both English and Dutch.

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Pa is moe en moe is moe. Broer is moe en zus is moe. Oom is moe, tante moe. Iedereen is moe. *Toon Hermans*

2

Diagnoses in patients presenting with fatigue: a one-year follow-up study

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Abstract

Background
While many studies have focused on 'unexplained' fatigue, little is known about the distribution of diagnoses that account for fatigue presented in primary care. We aimed to describe the diagnoses established within one year after the consultation that are likely to explain fatigue presented as a main symptom in primary care.

Methods
Prospective observational cohort study with one-year follow-up among adults presenting with a new episode of fatigue. Diagnoses were evaluated on the possibility of an association with presented fatigue, in a Delphi procedure and by GP expert opinion. After initial content-based evaluation, diagnoses were also evaluated by taking into account the time period between onset of fatigue and establishment of diagnosis.

Results
One fourth of 571 patients received a diagnosis that provided a plausible explanation for their fatigue; these diagnoses included both psychological problems (16%) and somatic diseases (8%). About one fifth of patients received symptom diagnoses, most often musculoskeletal problems, that could possibly explain the fatigue but for which there was no consensus regarding the association with fatigue. Except for infections, using the time period between onset of fatigue and establishment of diagnoses for the assessment of a plausible explanation proved to be difficult because of insufficient clinical information.

Interpretation
A minority of patients were diagnosed with serious pathology, and most patients did not receive a diagnosis that clearly explained their fatigue. Nevertheless, a wide range of the conditions and symptoms may explain or co-occur with the fatigue, indicating that it is a complex problem that deserves attention not only as a symptom of underlying specific disease.

Introduction

Fatigue is a non-specific symptom that is frequently presented as a main problem in primary care, with a prevalence ranging from 5-10%.[1-3] Both the nonspecific nature of the symptom and its high prevalence make fatigue a challenging complaint for GPs to deal with.

Fatigue may be a sign of a wide range of pathology, including respiratory, cardiovascular, endocrine, gastrointestinal, hematologic, infectious, neurologic and musculoskeletal disease, mood disorders, sleep disorders and malignancies.[4-13] Patients with a chronic disease often report symptoms of fatigue[14,15], and the prevalence of chronic disease in patients presenting with fatigue is high compared with other patients.[16] Thus, a proportion of patients presenting with fatigue may already have a diagnosed disease that (partly) explains their fatigue. Regardless of diagnosed pathology, fatigue is a phenomenon with multiple (social, physiological, psychological) dimensions.[17-20] Whereas many studies on fatigue have been performed in populations with chronic fatigue syndrome or otherwise 'medically unexplained fatigue', little is known about the distribution of diagnoses in populations of patients presenting with fatigue as a main symptom in primary care. A Dutch morbidity registration of episodes of care showed that fatigue remains a symptom diagnosis in around 40% of patients.[21]

Previous studies among patients presenting with fatigue as a main symptom either had rather small sample sizes[22,23] or reported diagnoses that were based on standardised laboratory testing at baseline.[24,25] Because of the wide range of possible diagnoses, large observational studies are needed to determine the distribution of diagnoses in primary care. These should include an assessment of the likelihood of an association with the presented fatigue.

We carried out a prospective study among patients presenting with fatigue as the main symptom. The course and prognosis of fatigue appeared to be diverse, and associated with many other factors including physical and emotional functioning, other symptoms, perceptions and social factors.[26,27] Our aim was to describe the distribution of diagnoses that were made in general practice within one year of follow-up, and are likely to be associated with fatigue presented as a main symptom.

Methods

Participants
We conducted an observational cohort study in 147 practices across the Netherlands among adult patients presenting with a new episode of fatigue, meaning they had not visited the GP for fatigue in the previous six months, nor before that for the same episode of fatigue. Fatigue as a presenting symptom was defined as complaints of tiredness or synonyms indicating fatigue such as exhaustion, but excluding more general complaints of 'malaise'. Patients who were receiving or had received chemotherapy or radiotherapy within three months before the consultation, and women who were pregnant or less than three months postpartum were excluded. Eligible patients were informed about the study by their GP and invited to participate. If interested, they were sent an information letter and baseline questionnaire. Patients were enrolled when they returned a signed consent form. Participating patients completed several questionnaires during the follow-up year (1,4,8,12 months after baseline) and gave separate informed consent to extract data from the GP's medical records. The study was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam, the Netherlands.

Data collection
All diagnoses made during the follow-up year, as well as pre-existing chronic diseases at the time of consultation, were extracted from general practice medical records. Data extraction regarding chronic diseases was limited to those conditions that could be related to fatigue and which could be assumed to be current at the moment of presentation of fatigue, regardless of treatment.

Association of diagnosis with fatigue
In order to obtain consensus on diagnoses that may be associated with fatigue, we performed a Delphi procedure[28] by e-mail in two rounds. A panel of eight experts (3 GPs, 2 internists, 1 GP specialised in infectious diseases and 1 physician-researcher) - not involved in the enrolment of patients - received a list of new diagnoses from the first 100 participating patients together with a list of diagnoses derived from the literature that could account for fatigue. In each round, the panel members were asked first to indicate whether the diagnoses could provide a plausible explanation for fatigue presented as a main symptom. Diagnoses were included when at least 70% consensus existed. Secondly, the panel members were asked to indicate the time-period between onset of fatigue and the diagnosed condition, during which the diagnosis would still provide a plausible explanation. The outcome of the Delphi procedure was intended to be used as a reference to decide which diagnoses in our study population could provide an explanation for the presented fatigue. Diagnoses from other participants that were not

yet included in the Delphi sample, or on which no consensus was obtained, were evaluated by two GPs (HvdH, HdV). After the total procedure, three categories of diagnoses were distinguished: plausible diagnoses, possible diagnoses and diagnoses that did not provide an explanation.

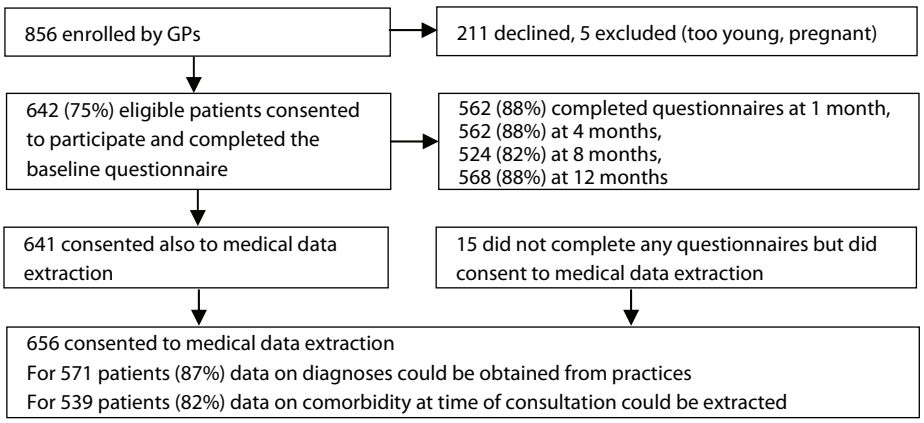
Diagnostic uncertainty
The GPs who enrolled the patients, indicated on the registration form to what extent they were certain about the cause(s) of the fatigue in the patient. GPs also recorded whether physical examination and diagnostic tests were performed or planned.

Analysis
Descriptive statistics were used to describe frequencies of diagnoses, comorbidity, (degree of) diagnostic uncertainty and initial management by the GP, and patient characteristics.

Results

Response
A total of 856 patients were initially enrolled by the GPs, of whom 642 patients consented to participate and returned the baseline questionnaire. All but one of these patients also consented to data extraction from their GP's medical records. Additionally, fifteen patients who did not complete the baseline questionnaire did consent to medical data extraction (see flow chart; figure 2.1). We were able to obtain data on diagnoses from 571 patients (87%); patient characteristics for this sample from the baseline questionnaire are shown in Table 2.1.

Figure 2.1 Flow chart of patient participation and data collection



Evaluation of diagnoses

A wide range of diagnoses was made within the year following consultation, representing all categories of the International Classification of Primary Care (ICPC). In total, 142 patients (25%) received a diagnosis that according to the panel provided a plausible explanation for the presented fatigue (196 diagnoses in total; Table 2.2); 126 patients in the cohort (22%) only received a 'possible' diagnosis (182 diagnoses; Table 2.3). The remaining 304 patients (53%) did not receive a diagnosis that was considered to provide a possible or plausible explanation for fatigue presented as a main symptom.

Table 2.1 Patient characteristics (self-report; baseline questionnaire)

	Number of patients (%); total n=571
Age (mean, SD)	43 (16)
Gender (female)	422 (74)
Duration of fatigue (n=546)	
<1 months	44 (8)
1-3 months	87 (16)
3-6 months	98 (18)
6-12 months	103 (19)
>1 year	214 (39)
Localisation of fatigue (n=556)	
Primarily head (mental fatigue)	91 (16)
Primarily extremities	46 (8)
Whole body, or head and extremities	362 (65)
Not clear	57 (10)
Psychological symptoms (4DSQ); elevated score (n=556)	
Distress	338 (61)
Depression	131 (24)
Anxiety	52 (9)
Sleep problems (SCL90); elevated score (n=556)	365 (66)
Number of other symptoms (IPQ-R, mean (SD) from 13 listed physical symptoms)	4.3 (2.7)
Attribution stress or worry (n=551)	307 (56)
Prolonged difficulties (n=556)	458 (82)
Mean score (SD), combining number and severity (range 0-25)	4.3 (4.3)
Severe difficulties in at least one area	105 (19)
Expectation that GP is able to find the cause of the fatigue (n=548) (yes)	287 (52)
Satisfied with GP's management of the fatigue during consultation (n=552) (yes)	504 (91)

Diagnoses thus identified, providing a plausible or possible explanation for fatigue, stemmed from all ICPC categories except eye, ear, urinary tract or male genital organs. Most frequently recorded somatic diagnoses were musculoskeletal problems (n=111, 20%), diseases or symptoms of the digestive system (n=46, 8%), nervous system (n=38, 7%) and respiratory tract (n=28, 5%). The majority of diagnoses reflected symptoms or

signs only, and no more than 47 patients (8%) received one or more diagnoses of clear somatic pathology (anaemia, pulmonary pathology, thyroid dysfunction, diabetes mellitus, coeliac disease, vitamine B12 deficiency, heart failure, angina pectoris, malignancy, rheumatoid arthritis, medication side effect). A total of 94 patients (16%) received a diagnosis indicating psychological problems or social difficulties. Of all diagnoses, only stress or neurasthenia was often recorded directly during the initial consultation when fatigue was presented.

Further evaluation by including time frame

Estimation of the maximum period of time between onset of fatigue and establishment of diagnosis that would allow the diagnosis to provide a plausible explanation for the fatigue resulted in a wide range in many cases and most members of the panel reported considerable difficulty in evaluating the timeframe. Therefore, the relevant time frame for all diagnoses was evaluated again by three GP-researchers (including two of the co-authors HvdH, HdV), taking into account both the duration of the fatigue at presentation and the time between consultation and diagnosis. However, the lack of additional clinical information (e.g. on the severity of the diagnosed condition and co-occurring symptoms), made it impossible to reliably estimate this time-period for most diagnoses. Therefore, we limited the assessment of timeframe to infections, for which consensus existed: both fatigue and time to diagnosis should be of a short duration, with fatigue lasting not longer than one month, and diagnosis of infection established within two weeks after the consultation. Infections were frequent (n=104, 18%); however, when considering the maximum timeframe, in only two cases infections could provide a plausible explanation for the presented fatigue (Table 2.2).

Comorbidity

Conditions that were known to be current at presentation are presented in Table 2.4. In total, 58 patients had a concurrent disease that could explain the fatigue. Most frequently recorded comorbid diseases were asthma or COPD (37) and diabetes (17). Fourteen patients were known to have a malignancy in their medical history, and for 20 patients a functional syndrome, mostly IBS (17), had been recorded.

Table 2.2 Diagnoses providing a plausible explanation for fatigue presented as a main symptom

Diagnosis category (ICPC code)	Frequency (n patients; total n=571)	Frequency of diagnoses recorded during the consultation when fatigue was presented
Psychological or social (P or Z)	94 (16%)	
Depressive symptoms or depression#	28	4
Strain, neurasthenia, burn-out	31	15
Anxiety#, tension#, hyperventilation (R), distress or worry#	25	4
Sleeplessness or sleeping problems	11	1
Family or relationship problems#	9	1
Psychological problems	5	2
Loss or mourning	4	1
Affective psychosis	1	0
General (A)	22 (4%)	
Anaemia#	9	3
Medication side effect#	6	1
Chronic Fatigue Syndrome	4	0
Chronic pain syndrome or widespread pain	3	1
Viral infection* (unspecified)	2	2
Respiratory tract (R)	15 (3%)	
Asthma#, COPD#, decreased pulmonary function or chronic bronchitis, including exacerbations	12	1
Chronic sinusitus	3	0
Endocrine system/metabolism/diet (T)	15 (3%)	
Hypothyreoidism#	7	1
Diabetes Mellitus	4	0
Hyperthyreoidism#	3	0
Coeliac disease	1	0
Vit B12 deficiency#	1	0
Digestive system (D)	12 (2%)	
Irritable Bowel Syndrome	12	2
Female genital organs (X)	6 (1%)	0
Climacteric symptoms#	6	0
Cardiovascular system (K)	5 (<1%)	
Heart failure	3	0
Angina Pectoris	3	0
Malignancy# bladder (U), leukemia (B), melanoma (S), colon (D)	4 (<1%)	0
Musculoskeletal system (L)	2 (<1%)	
Rheumatoid arthritis or Myalgica Rheumatica	2	0

#Consensus in the Delphi panel. *Included out of n=104 with infection diagnoses, after taking account of the timeframe between fatigue and diagnosis. ICPC=International Classification of Primary Care; 4DSQ=Four-dimensional Symptom Questionnaire; SCL-90=Symptom Checklist-90; IPQ-R= Illness Perception Questionnaire-Revised.

Table 2.3 Diagnoses providing a possible explanation for fatigue presented as a main symptom

Diagnosis category (ICPC code)	Frequency (n patients); total n=571	Frequency of diagnoses recorded during the consultation when fatigue was presented
Musculoskeletal system (L)	108 (19%)	
Back problems	35	2
Neck problems	20	1
Joint problems in the extremities	42	0
Myalgia*	21	2
Non-cardiac chest symptoms	8	0
Osteoarthritis	7	0
Digestive system (D)	36 (6%)	
Abdominal pain or symptoms (upper / lower)	23	0
Diarrhea	8	1
Constipation*	5	0
Abnormal liver function	1	0
Nervous system (N)	38 (7%)	
Headache	13	2
Dizziness	11	1
Chronic Tension Type Headache	8	2
Migraine	3	0
Polyneuropathy	2	0
Concussion*	2	1
Respiratory tract (R)	13 (2%)	
Cough	9	1
Upper airways or throat symptoms	3	0
Dyspnea*	2	0
General (A)	6 (1%)	
Hay fever, rhinitis, allergy*	6	2
Cardiovascular system (C)	6 (1%)	
Arrhythmia	3	0
Cardiac symptoms	2	1
Intermittent claudication*	1	0
Skin (S)	3 (<1%)	
Itch*	3	0
Endocrine system, metabolism, diet (T)	1 (<1%)	
Obesity*	1	0

*No consensus on plausibility of providing an explanation for presented fatigue. No asterisk indicates that consensus existed on a lack of information to assess plausibility of providing an explanation; ICPC=International Classification of Primary Care.

Table 2.4 Comorbidity and medical history

	Number of patients (total n=539)
Current chronic conditions at the time of consultation	58 (11%)
Asthma /COPD	37 (7%)
Diabetes	17 (3%)
Arthritis	3
Ulcerative colitis	2
Renal failure	1
Thalassemia	1
Stickler syndrome	1
Malignancy (ever)	14 (3%)
Functional syndrome (ever)	20 (4%)
Irritable bowel syndrome	17 (3%)
Fibromyalgia	2
Whiplash	2
Chronic Pain Syndrome	1

Diagnostic uncertainty

In the majority of cases, GPs performed diagnostic tests, and most GPs had at least some idea about possible causes of the fatigue at first presentation (Table 2.5). Most patients were satisfied with the way the GP managed their problem, and half of the patients expected that their GP could establish the cause of their fatigue (Table 2.1). In 31% of cases, the GP had at least some idea about the cause of fatigue while the patient did not expect the GP to provide a diagnosis, and in 15% of cases, the GP had no idea while the patient did expect a cause could be established. Patients' satisfaction with GP management was not related to the GP performing diagnostic tests (Pearson χ^2, p=0.24) or physical examination (p=0.69).

Table 2.5 Diagnostic uncertainty

	Number of patients (%)
Degree of certainty of the GP about possible causes of the presented fatigue (n=551)	
Quite certain	154 (28)
Some idea	228 (41)
No idea	169 (31)
Physical examination performed or planned	305 (55)
Laboratory or imaging tests performed or planned (n=552)	485 (88)
Reasons to do so (n=464)	
only fatigue	233 (50)
(partly) another symptom*	103 (22)
(partly) request of patient*	132 (28)

* Not mutually exclusive.

Discussion

Diagnoses explaining fatigue

The wide range of diagnoses reflects evidence from the literature and practical experience regarding the differential diagnosis of fatigue. New diagnoses providing a plausible explanation for presented fatigue were more often psychological problems (16%) than somatic diseases (8%). The diagnoses providing a possible explanation encompassed a range of symptom diagnoses.

The small proportion of patients receiving a diagnosis of somatic pathology corresponds with findings of previously published smaller cohort studies in primary care.[24,25,29] These studies, however, used stricter inclusion criteria (mostly initially unexplained fatigue), excluded cases with existing chronic disease[22,24,29], or reported on diagnoses based on laboratory tests only.[24,25] Two studies[22,30], one of which only included 52 patients, reported higher percentages of somatic diagnoses (45% and 51%). A major difficulty in comparing results from these studies with our findings is the general lack of information in previous studies on the assessment of diagnoses that were considered to explain the fatigue.

Among the pre-existing chronic diseases that were likely to be current at the time of consultation, respiratory conditions were more frequent in our cohort compared to prevalence rates in primary care.[15] It should be noted that our fatigued population included less elderly patients compared to a national morbidity registration[31], which may affect the number of chronic (respiratory) conditions.

Symptom diagnoses

One fifth of patients were diagnosed with a (mostly nonspecific) musculoskeletal problem during the follow-up year. The association of such symptoms with fatigue has been reported in a general population survey.[32] In a large recent study among patients primarily from primary care[33], fatigue was very common, and symptom clusters were identified, including musculoskeletal symptoms. However, these clusters showed considerable overlap, and were not specifically related to fatigue.

Symptom diagnoses are generally not presented in overviews of differential diagnoses for fatigue, and information on symptom clusters in primary care populations is scarce. However, the recognition that the majority of patients in primary care present with (multiple) symptoms that cannot be explained by a specific disease, and that the severity of presented symptoms is part of a continuum regardless of an established diagnosis, has brought the need to attention for more research based on symptoms.[34,35] Practical suggestions have been made for a categorisation based on severity of symptoms that are 'medically unexplained'.[36]

The severity and duration of symptoms co-occurring with fatigue may vary widely, which is not apparent from the recorded diagnoses only. This was the reason that the

panel members often concluded that there was insufficient information to assess the plausibility of a direct association with fatigue. The fact that virtually none of these diagnoses were established during the consultation raises questions on the temporal association between fatigue and musculoskeletal or other symptoms. As most symptoms may show a recurrent pattern over time, further research is needed to help clarify the association between fatigue and other nonspecific symptoms.

Psychological and sleep problems

A substantial part (46%) of diagnoses providing a plausible explanation for fatigue were psychological problems (16% of all patients). However, this number may still be an underestimation. Results from the patient questionnaires showed that a quarter of patients had elevated levels of depressive symptoms, and a majority had elevated distress scores[26], which is far more than the minority who received such diagnoses from their GP. Furthermore, other studies have reported psychological symptoms in the majority of fatigued patients.[37-39] Due to the variation in the way GPs recorded or coded diagnoses, it is possible that psychological problems were recognised, but not explicitly recorded as diagnoses.

Sleep problems were reported in only 2% of cases. This number is in high contrast to the sleep problems reported by a majority of patients in the questionnaires.[26] As with psychological symptoms, problems with sleep might either not be recognised or not recorded.[40-42] Sleep problems may be perceived by GPs as a lifestyle issue (or) evidently related to fatigue, and therefore not recorded as a diagnosis.

Evaluation of our approach

At least half of the patients did not receive a diagnosis that could explain their fatigue, which suggests that the fatigue remains 'medically unexplained' in many cases. This is consistent with previous findings.[21] However, the lack of a medical explanation does not always imply that there is no explanation. Considering the results of the patient questionnaires, other (psychosocial) factors, although not registered in the medical records, are likely to play a role in the fatigue of many patients.

About 50% of all patients did receive a diagnosis that might explain their fatigue, but for most diagnoses it proved to be too difficult to assess the association with fatigue, even when considering the time period between fatigue and diagnosis. The severity of a symptom or disorder can make a relationship with fatigue more plausible. Moreover, we did not know how tired patients were at the time of diagnosis. Asking the participating GPs themselves to record which diagnoses provided a possible explanation for their patient's fatigue would be a useful complementary method to answer our research question.

Infections

For infections we were able to make a clearer estimation of the association with presented fatigue. Infections are part of the differential diagnosis of fatigue and the incidence in patients visiting for fatigue has been reported to be high.[21,30] Yet, only few patients in our study received a diagnosis of infection during the consultation or soon after, which makes it unlikely for the majority of infections to provide an explanation for the presented fatigue. Most patients were already chronically fatigued at presentation (61%), and this was also the case for those who were diagnosed with an infection at any time during follow-up (58%).

We did not ask whether patients had had an infection shortly before they presented with fatigue. However, prospective studies on postviral fatigue have shown that common (upper respiratory tract) infections are not associated with the development of fatigue, while previous fatigue can be a strong predictor of the occurrence of viral infections.[43,44] The odds of infections following fatigue were larger than the odds of fatigue following infections in a study comparing the possibilities for longitudinal relationships.[45] Although the Epstein Barr virus was shown to be associated with later fatigue in some studies[44,46], previous fatigue was not assessed in these studies. Others found that prolonged fatigue after triggering infections was associated with severity of the acute illness or symptoms, rather than the specific pathogen.[47] These findings indicate that fatigue may play a role in making people more prone to an infection.

Strengths and limitations

To our knowledge, a survey of diagnoses in a large cohort of patients presenting with fatigue in primary care has not been performed before. Although we did not have all necessary information to establish a definite association with presented fatigue, we could make a more precise assessment for the role of infections by taking into account both the duration of fatigue and date of diagnosis. Furthermore, we showed which diagnoses were made during the consultation when fatigue was presented, and which were made later on during the follow-up year.

This study was observational and therefore the diagnoses represent those made and recorded in daily practice by individual GPs; we did not use a standardised protocol for physical examination or diagnostic testing. As GPs differ in their decision making regarding diagnostic procedures and referrals, this will have resulted in variation in recorded diagnoses.

Data on current comorbidity are important to provide when presenting an overview of diagnoses. We were able to show that respiratory conditions and diabetes were more often current comorbidities than newly diagnosed conditions. Our data were not comprehensive however, therefore we may not have identified all conditions that may have contributed significantly to the presented fatigue. Furthermore, patients presenting with fatigue may have several concurrent conditions.

Conclusion

This observational study among patients presenting with fatigue in primary care showed a wide variation of diagnoses, but the prevalence of severe pathology was low. The number of psychosocial problems was relatively high, and may partly explain fatigue in this primary care population. These symptoms, including sleep problems, showed a large discrepancy with self-reported data. Practitioners should address these problems in patients presenting with fatigue.

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Doctors take care of people, some of whom have diseases and all of whom have some problem. *Eric Cassell*

3

Prognosis of fatigue: a systematic review

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Abstract

Objective
The objective of the study was to summarize evidence on the course and prognostic factors of fatigue in primary care patients and in the community.

Methods
Two reviewers independently screened identified citations, discussed eligible studies, and assessed methodological quality of selected studies. Data concerning study population, duration of follow-up, measurement of fatigue, outcome, and prognostic factors were extracted. Studies with populations selected by a specific disease or postpartum condition were excluded.

Results
We selected 21 articles reporting on 11 (partly) primary care cohorts and six community cohorts. Follow-up was up to 1 year in primary care and up to 4 years in the community, and in most studies that presented duration of fatigue, participants were chronically fatigued. Because of wide heterogeneity of studies, a qualitative analysis was performed. Recovery of fatigue varied widely, but no differences were found between settings. Sufficient evidence for an association with recovery was found for lower severity of fatigue, and limited evidence was found for good self-reported health, mental health, and psychological attributions. A major deficit in methodological quality of most studies was a potential bias due to low or selective response or loss to follow-up.

Conclusion
Most studies on fatigue included patients with long symptom duration at baseline, making it difficult to study prognosis early in the course of fatigue. To provide clear evidence on prognosis in fatigued persons, prognostic studies should use an optimal design including selection of an inception cohort with limited duration of fatigue at baseline, a sufficient sample size, and information on rates and selectivity of response and loss to follow-up.

Introduction

Fatigue is common in the community and a frequently presented symptom in primary care. The two-week prevalence in a community-based sample of 12.672 people was 36%[1]; in primary care the annual incidence of fatigue presented as a symptom ranges from 1.5-2.6%,[1-3] while a prevalence of 25% has been reported.[4]

Fatigue is an intriguing phenomenon, which occurs in a variety of diseases and is seldom explained by a specific condition. When presented in primary care, GPs focus on co-occurring symptoms and mostly adhere to a wait-and-see policy. However, identification of patients with a poor prognosis who need special attention is important. Therefore, information about prognostic factors is needed in order to better predict the course of fatigue in relevant subgroups of patients and subsequently facilitate management decisions.

Reviews on the prognosis of fatigue have focused mainly on selected patients, notably the chronic fatigue syndrome (CFS)[5], rather than fatigue as a common symptom in primary care or the general population. Joyce et al. reviewed the literature on fatigue in 1996 in a wide variety of patient populations, but the majority of studies was hospital-based.[6] They report on ten studies of fatigue presented in primary care, which showed a wide variety in outcome, with recovery or improvement ranging from 22 to 97%. Limited evidence was presented on fatigue in the community. However, a major limitation of the review is that methodological quality of the studies was not taken into account.

The aim of this study was to perform a systematic review of the literature on the course of fatigue and to identify indicators of outcome in fatigued patients in primary care and in the community. Including community studies may provide more evidence on prognostic factors, since we do not expect predictors of outcome to be much different in patients visiting the GP or not. As to the course however, we expect that there is a difference between both populations, either in favour of consulting patients because of attention and management of their problem, or in favour of those not visiting the GP because their fatigue might be less severe.

Methods

Identification and selection

Studies were identified by systematic searches of Medline (1966 through October 2006), Psycinfo (1967 through October 2006) and Embase (1966 through October 2006). The search strategy consisted of key words and MeSH headings relating to fatigue, setting

(general practice or community) and journal titles for general practice (Medline). Studies in English, Dutch, German and French were included. Additionally, a Dutch journal for research in primary care (Huisarts en Wetenschap) was searched using the keyword fatigue (1987 through October 2006).

Title, abstract and full text of identified papers were screened for eligibility by two reviewers (IN and HvdH). References of selected articles were checked for additional eligible papers which had not been identified by the computerized search. The following criteria were applied for selection:

- Participants in the study were fatigued at baseline
- The study was carried out in general practice or the community, including occupational settings
- The population was not selected by a specific disorder or disease, or post-partum condition, nor by a diagnosis of CFS
- The study had a longitudinal and prospective design
- The study presented level of fatigue as outcome
- Results were published as a full report

Quality assessment

Methodological quality was assessed independently by two reviewers (IN, HvdH). Disagreement between the reviewers was resolved during a consensus meeting. No standard assessment method is currently available for reviewing the methodological quality of prognostic studies. The checklist we used was based on a standardized checklist used by Licht et al[7], and contains 14 items on five categories: participation bias, attrition bias, outcome measurement, prognostic factor measurement, data presentation and analysis, largely based on categories of bias described by Hayden et al (Table 3.1).[8] We added two criteria concerning participation bias from the checklist suggested by Hayden et al: 'description of study population' should include inclusion criteria, and articles should provide an adequate description of recruitment. Additionally, an item on representativeness of the study sample was added from a checklist used by Pengel et al.[9]

Data extraction

Data were extracted from eligible papers on study population, design, setting, duration of follow-up, measurement and duration of fatigue, improvement or recovery, prognostic factors and strength of association with recovery. We also recorded the presentation of any functional outcomes (e.g. physical functioning, work productivity). The results were stratified by setting (primary care and community); primary care was further stratified by patients consulting for fatigue and studies among patients consulting the GP for any reason.

Table 3.1 Criteria for assessing methodological quality*

Criteria	Score
Study population / participation bias	
A. Description of cohort/study population	+ / -
B. Measurement of fatigue	+ / -
C. Recruitment of subjects adequately described	+ / -
D. Representative sample	+ / -
E. Response rate ≥ 75%	+ / -
F. No selective response	+ / -
Attrition bias	
G. Loss-to-follow-up < 20%	+ / -
H. No selective loss-to-follow-up	+ / -
Outcome measurement	
I. Follow-up of at least 3 months	+ / -
J. Similar assessment of fatigue outcome	+ / -
Outcome measurement	
I. Follow-up of at least 3 months	+ / -
J. Similar assessment of fatigue outcome	+ / -
Prognostic factor measurement	
K. Standardised assessment of potential prognostic factors	+ / -
Data presentation and analysis	
L. Frequencies of outcome measures presented	+ / -
M. Frequencies of prognostic factors presented	+ / -
N. Univariate or multivariate estimates of prognostic factors presented	+ / -

*The criteria are based on checklists used by Licht et al, Hayden et al and Pengel et al.[7-9] For the applied list explaining the criteria, see appendix. 'positive' (+) indicates sufficient information and a positive assessment; 'negative' (-) indicates bias; '?' means it is not clear because of insufficient information.

If not provided in the article, univariate associations between prognostic factors and outcome in terms of Odds Ratios with 95% confidence intervals were calculated if sufficient data were available. This was done because most articles presented results in Odds Ratios. Outcomes presented in terms of poor prognosis were converted into recovery outcomes.

Analysis

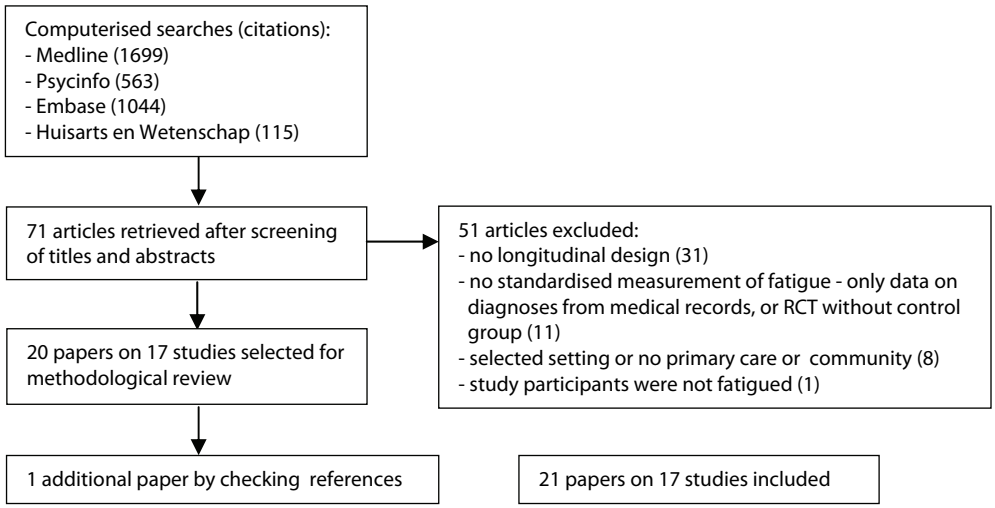
The studies we identified were heterogeneous in many aspects, such as measurement of fatigue, composition of study population and assessed predictors. Therefore, a quantitative analysis of the results was not possible, and we performed a descriptive qualitative analysis, taking into account the number of studies, methodological quality according to scores on different criteria of the checklist, sample size, and consistency of results. Our definition of a positive outcome ('recovery') included outcomes of improvement or substantial improvement, when no data on recovery were available.

Results

Selection of studies

The search resulted in 3162 citations, of which 71 papers were retrieved after screening of title and abstract (Figure 3.1). Twenty of these met our selection criteria. The main reason for exclusion at this stage was a cross-sectional design. One additional paper was identified by checking references of selected papers. Finally, 21 papers were included reporting on 17 studies. Four studies reported on primary care attenders presenting with symptoms of fatigue and six reported on patients visiting the GP for any reason. Another six studies reported on fatigue in the general population, three of which specifically addressed employees. One study reported on both primary care and the general population.

Figure 3.1 Selection of studies



Methodological quality

The two reviewers initially agreed on 75% of all items in the quality assessment. Most disagreements concerned items on presented frequencies of outcome and prognostic factors (41% agreement). In Table 3.2, the results of the methodological assessment are presented. One study was described in four papers, two of which were not further considered because they presented information on selected subgroups of the study population or had an explanatory rather than a predictive design[10,11]; the other two articles were assessed together, as they concerned the same study.[12,13] Another study was described in two articles, which were also assessed in combination.[14,15]

Table 3.2 Results of methodological assessment of prognostic cohort studies on fatigue

	No participation bias						No attrition bias		Outcome and prognostic factor measurement			Data presentation and analysis		
First author	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Primary care														
Nelson et al[18] (1987)	+	+	+	+	?	?	+	-	+	+	+	+	-	-
Valdini et al[24] (1988)	+	+	+	+	n.a.	n.a.	-	-	+	+	?	+	+	+
Kroenke et al[22] (1988)	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Cathebras et al[19] (1992)	+	-	+	+	?	?	-	-	+	-	+	+	+	-
Valdini et al[17] (1989)	+	+	-	?	?	?	+	+	+	?	+	+	-	-
Hickie et al[21] (1999)	+	+	+	+	?	?	n.a.	n.a.	+	+	+	+	+	+
Skapinakis et al[23] (2003)	-	+	+	-	n.a.	n.a.	-	-	+	+	+	+	+	+
Ridsdale et al[16] (1993)	+	+	+	?	+	?	+	-	+	+	+	+	+	+
Bates et al[20] (1993)	+	+	+	+	-	?	+	?	+	?	+	+	-	-
De Ridder et al[37] (2004)	+	+	+	+	n.a.	n.a.	n.a.	n.a.	-	+	+	-	-	-
Mixed population														
Bentler et al[38] (2005)	+	+	-	-	n.a.	n.a.	+	+	+	+	+	+	-	-
Community														
Buchwald et al[25] (1995)	+	+	+	+	-	-	+	?	+	+	+	+	-	-
Chalder et al[39] (1996)	+	+	+	+	?	?	-	?	+	+	+	-	+	+
Eriksen et al[26] (2006)	+	+	+	+	n.a.	?	+	+	+	+	+	+	-	+
Taylor et al[27] (2002)	+	+	+	+	n.a.	n.a.	n.a.	+	+	+	+	+	+	+
Huibers et al (2004, JOEM[12] and 2004, JECH[13])*	+	+	+	+	n.a.	n.a.	+, n.a.	-, n.a.	+	+	+	+	-, +	+
Huibers et al (2004, JPR[14]) and Leone et al (2006[15])*	+	+	+	?	n.a.	n.a.	+	?, -	+	+	+	+,-	-	+,-
Number of + scores per item	16	16	15	12	1	1	10	5	16	14	16	14	9	10

n.a. = not applicable. * Two articles concerning the same study. Item scores are mostly similar and therefore combined; in case of different scores on the same item, the two scores are presented.

Most studies scored positive on description of the study population, standardised measurement of fatigue and recruitment of subjects. Twelve studies had a representative sample. However, the response rate of eligible (fatigued) participants was unknown in all but one study; this was mostly due to the fact that selection of *fatigued* persons took place only after first including a broader population for which a response rate was presented. Consequently, it was unclear whether there had been any selective non-response among fatigued patients. Attrition bias was likely in half of the studies, as only ten studies reported less than 20% drop-outs, and only five studies provided data demonstrating no selective loss to follow-up. Most studies scored positive on measurement of outcome and prognostic factors. Frequencies of prognostic factors were presented in nine studies, and prognostic estimates were presented or could be calculated in ten studies.

Since the studies most differed in attrition bias, which we consider to be an important aspect of prognostic study design, we decided to take this aspect into account when interpreting results regarding course and prognosis. Attrition bias was considered to be unlikely ('plus') in studies demonstrating no selective loss to follow-up (positive score on item H), and in studies with limited loss to follow-up (<20%) that did not provide information on selective drop-out (item G positive, item H unclear). Prognostic factors with consistent and significant results in at least two studies with a minimum sample size of approximately 100, and a 'plus' on attrition bias were considered to be underpinned by sufficient evidence.

Course of fatigue

In Table 3.3, an overview of extracted data is presented. Fifteen studies presented frequencies of fatigue outcome; the duration of follow-up varied from six weeks to four years.

Primary care

In the primary care studies, follow-up was limited to one year. For patients consulting the GP for fatigue (n=22-207), short term recovery varied from 41% after 6 months[16] to 23% after 7 months[17], one-year recovery varied from 30 to 51%.[18,19] Recovery from fatigue in patients visiting the GP for any symptom (n=26-1306), all having a one year-follow-up, varied from 22 to 80%.[20-24] The three studies in primary care presenting lowest recovery rates received a positive evaluation of attrition bias[17,20,22], however two of these included very small sample sizes.[17,20]

Community

Community studies had a longer-term follow-up. Recovery or improvement in these studies varied from 22 to 55%.[12-15, 25-27] Attrition bias was considered unlikely in four studies with the same range of recovery rates.[14,25-27]

In both settings, similar differences in study characteristics were apparent between studies reporting lowest and highest recovery rates. Most studies reporting low recovery rates had small sample sizes (n=22, 26, 74)[17,20,25] consisting of chronically fatigued persons, whereas studies reporting higher recovery rates described large cohorts (n=1306 or 2108)[12,13,23], did not present duration of fatigue at baseline and scored negatively on attrition bias.

Most studies had only one follow-up assessment of fatigue outcome. Only two studies in primary care and two among employees had more than one measurement of fatigue outcome during follow-up; most of these studies showed attrition bias. In primary care, rates of recovery increased from 19% to 41% at two weeks to six months after baseline[16], and from 27 to 51% at three to twelve months.[18] Recovery at six months was around

40% in both studies. In employees, rates of recovery increased from 39% (4 months) to 77% (2 years)[12,13], and from 34% (4 months) to 43% (1 and 4 years).[14,15]

Three studies also reported on functional outcomes. One primary care study showed a slight improvement in the number of patients without limitations in physical functioning from 15% (baseline) to 30% (1 year) for main symptom fatigue and rates of 19 to 40% in waiting room patients.[18] Two community studies among employees reported on work productivity. Among employees not on sick leave, sickness absence increased from 1.8% after four months to 3.1% after two years.[12] Among employees who were on sick leave, 55% (4 months) to 62% (1 year) resumed work[14], whereas 26% deteriorated to complete work incapacity after four years.[15]

Prognostic factors predicting recovery

Prognostic estimates of improvement or recovery from fatigue were presented or could be calculated in seven primary care studies and four community studies. All associations are summarized in Table 3.4, along with information on drop-out and attrition bias. Regarding fatigue characteristics, duration was analysed and presented as a prognostic factor in only one primary care study. This study reported a significant association with poor outcome for fatigue with a minimum duration of three months at baseline.[16] In another study the authors report that fatigue outcome was slightly worse in patients fatigued for six months or more, but insufficient data were presented to calculate an association.[19] Both studies showed attrition bias. Fatigue severity was assessed and significantly associated with poor outcome in one primary care study and three community studies. Two studies showed attrition bias; in one of these, drop-outs were more fatigued than those who remained in the study, which may have resulted in an underestimation of the strength of this prognostic factor.

Table 3.3 Course and prognosis of fatigue

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
A. Primary care					
Patients presenting with fatigue					
Nelson et al[18] (1987) Cohort study	113 pts with main presenting symptom fatigue for ≥ 1 month (CCF group), 116 waiting room pts scoring < 14 on Vitality Scale (QF group) · England · Mean age: 52 · 69% women · Duration: mean 17 months	3 months, 6 months, 1 year Vitality Scale · Drop-out 26% (11% at t=3 months) · Completers more often married and higher rate of employment	Fatigue recovery CCF group 27% (3 months) 42% (6 months) 51% (1 year) (improvement 16%) QF group 29% (3 months) 35% (6 months) 35% (1 year) No limitations physical functioning (baseline, 3 months, 6 months, 1 year) CCF group 15%, 30%, 39%, 30% QF group 19%, 27%, 41%, 40% No limitations emotional functioning CCF group 21%, 30%, 45%, 46% QF group 17% 30%, 39%, 38%	-	-

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Ridsdale et al[16] (1993) Cohort study	207 patients with main complaint fatigue for > 2 weeks, > 15 years old and 200 controls · England · Mean age: 43 (whole cohort) · 75% women (whole cohort) · Duration: 74% > 6 months	2 weeks, 8 weeks, 6 months Fatigue questionnaire (Chalder) · Drop-out: 17% · Completers were older	no high fatigue score 19% (2 weeks, visit) 34% (8 weeks, (questionnaire) 41% (6 months)	Independent associations: · Previous episodes of anxiety or depression · Duration of tiredness > 3 months · Age · Gender (female) · Occupation - manual - unemployed Adjusted for age, gender, occupation: · GHQ score >2	 OR= 0.34 (0.16-0.69)* OR= 0.47 (0.24-0.93)* OR= 1.00 (0.98-1.02) OR= 2.27 (0.98-5.26) OR= 0.58 (0.24-1.39) OR= 0.96 (0.36-2.56) OR= 0.65 (0.32-1.32)
Cathebras et al[19] (1992) Cohort study	93 pts presenting with fatigue as a main or co-occurring symptom, age 18-75 years · Canada · Mean age: 43 · 66% women · Duration: 42% > 6 months 58% < 6 months	1 year Baseline: patients' and/or GP's mention of fatigue as a presenting complaint Outcome: 2 questions used 1) fatigued in last 3 months? (<SIQ) 2) tired for >2 weeks in past 12 months? (<DIS) · Drop-out: 28% · Completers less depressed	1) 30% not fatigued in past 3 months 2) 49% not tired > 2 weeks in past 12 months	-	-
Valdini et al[17] (1989) Cohort study	22 pts visiting for main symptom fatigue, duration > 1 year, cause uncertain · USA · Mean age: 44 · 64% women · Duration: mean 12 years	At least 3 months, on average 7 months Baseline: RAND vitality index Outcome: ? · Drop-out: 0%	23%	-	-

Table 3.3 (continued)

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Primary care attenders					
Kroenke et al[22] (1988) Cohort study	102 waiting room pts with fatigue as major problem for > 30 days, medically unexplained · USA · Mean age: 57 · 66% women · Duration: 72% > 1 year	1 year Montgomery scale and Cardenas & Kutner scale · Drop-out: 0%	28% improvement	Age >64 years vs. younger 40-64 vs rest <40 vs. older SIP score <14 vs. higher ESR normal vs. abnormal	ORs calculated from presented frequencies OR=0.24 (0.08-0.76)* OR=1.95 (0.80-4.76) OR=2.12 (0.66-1.91) OR=3.35 (1.15-9.77)* OR=4.97 (0.61-40.4)
Valdini et al[24] (1988) Cohort study	115 waiting room pts scoring < 14 on RAND index of vitality (with 139 controls) · USA · Mean age: not presented · 72% women at follow-up (total cohort), baseline not presented · Duration: not presented, at least one month	1 year RAND index of vitality (RIV), score < 14 · Drop-out: 57% total cohort, 37% of fatigued patients · Completers: more elderly	42%	Race (white vs. non-white) Education (high school or college vs. less than high school)	ORs calculated from presented frequencies OR=12 (1.47-98.2)* OR=0.29 (0.10-0.83)*
Hickie et al[21] (1999) Cohort study	142 fatigued patients, scoring >2 on SOFA scale (and 510 controls) · Australia · Mean age: 40 (whole cohort) · 75% women (whole cohort) · Duration: not clear	1 year SOFA (Schedule of Fatigue and Anergia) adapted for primary care · Drop-out: not presented	42%	'anxiety/depression' (GHQ>4 and SOFA<3)	ORs calculated from presented frequencies OR=0.25 (0.12-0.52)*

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Skapinakis et al[23] (2003) Cohort study	1306 patients with prolonged unexplained fatigue, 487 with substantial unexplained fatigue, 389 with neurasthenia, all waiting room pts · 14 countries · Age: not presented · % women: not presented · Duration: not presented	1 year number of positive answers to 3 screening questions on fatigue during past month: tired all the time, easily tired while performing everyday tasks, minimal physical effort causes exhaustion. . Drop-out: 32% . Completers: less subjects scoring ≤20 on GHQ-28	Prolonged fatigue group: 61% Substantial unexplained fatigue group: 79% Neurasthenia group: 80%	Number of fatigue symptoms (1-3) prolonged fatigue substantial fatigue neurastenia For cases of prolonged fatigue at baseline Age Gender (female) GHQ-28 score Any chronic physical disorder Poor self-reported health Not married vs married 1-2 children vs no children >2 children vs no children Education - intermediate vs lower - higher vs lower Gross national income - middle vs low - high vs low	Test for trend OR= 0.66 (0.52-0.83)* OR= 0.42 (0.25-0.68)* OR= 0.52 (0.32-0.85)* OR= 1.00 (0.97-1.01) OR= 0.69 (0.47-1.00) OR= 0.96 (0.93-0.99)* OR= 0.91 (0.61-1.35) OR= 1.25 (0.75-2.13) OR= 0.69 (0.40-1.19) OR= 1.11 (0.67-1.82) OR= 0.82 (0.47-1.45) OR= 0.67 (0.37-1.22) OR= 1.47 (0.71-3.03) OR= 0.79 (0.44-1.43) OR= 0.96 (0.55-1.67)
De Ridder et al[37] (2004) Cohort study	221 patients fatigued for > 2 weeks and < 2 years · Netherlands · Mean age: 43 · 74% women · Duration: 40% > 6 months, 60% < 6 months	6 weeks MFI-20, physical fatigue scale · Drop-out: not presented	-	-	-

Table 3.3 (continued)

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
B. Mixed population					
Bentler et al[38] (2005) Cohort study	159 patients from either waiting room in primary care, members of a CFS association or patients visiting CFS presentations; unexplained fatigue, ≥ 6 months, >17 years old · USA · Age: 79% between 30-55 · 87% women · Duration: median 6.7 years	2 years (data available on 1.5 years: from 6 months to 2 years after baseline) RAND Vitality Index (3 questions) and Fatigue Severity Scale (2 questions) · Drop-out: 3%	11% substantial improvement 13% slight improvement	-	-
C. Community					
Buchwald et al[25] (1995) Cohort study	74 cases with 2 major criteria CFS, unexplained fatigue · USA · Mean age: 41 · 67% women · Duration: not presented (≥ 6 months)	2 years Baseline: Questionnaire containing questions on CDC criteria for CFS, 2 major criteria ('chronic fatigue') Outcome: ? · Drop-out: not presented Response rate only 37% · Participants relatively older, more men	22% after 1 year	-	-
Chalder et al[39] (1996) Cohort study	116 cases > 6 months fatigued score ≥ 3 on fatigue questionnaire, with attribution of either ME (38), psychological (40) or social (40). · England · Mean age: 36 · 73%, 46%, 19% women · Duration: mean 3.5 years (ME), 7 months (psychological group), 1.7 years (social group)	18 months Fatigue Questionnaire (Chalder et al, 1993) · Drop-out: 22% (17%, 13%, 26%) · ME group less patients married or living together, more fatigued; psychological group higher GHQ scores	No proportions presented	Gender and marital status Higher GHQ score Fatigue attribution (ME or psychological vs. social)	Explained variance for a *higher fatigue score* R^2=0.04 p<0.05 R^2=0.11 p<0.001 R^2=0.15 p<0.001

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Eriksen et al[26] (2006) Cohort study	691 nurses' aides working ≥ 18 hours/week, not on leave because of pregnancy or illness, usually or always fatigued during past 14 days · Norway · Mean age: not presented · 96% women · Duration: not presented	15 months Single question on fatigue during past 14 days · Drop-out: 16%	55%	Being bothered a lot by long term health problems of any kind vs. no long term health problems	OR=0.49 (0.32-0.77)*
				Feeling always fatigued vs. usually fatigued during the previous 14 days	OR=0.34 (0.19-0.60)*
				Positive challenges in job, 3rd quintile vs. lowest quintile (QPSNordic)*	OR=2.16 (1.27-3.69)*
				Support from immediate superior, 3rd quintile vs lowest quintile*	OR=0.45 (0.24-0.85)*
				Feedback about one's quality of work, rather seldom vs. never or seldom*	OR=1.96 (1.19-3.22)*
				* of all quintiles, significant associations are presented Note: associations very specific for this work setting are not presented	
Taylor et al[27] (2002) Cohort study	51 cases fatigued for ≥ 6 months, ≥ 18 years old · VS · Mean age: 45 · 76% female · Duration: mean 3 years	2 years Fatigue Scale (Chalder et al) · Drop-out: not presented	49%	Fatigue severity score Fatigue is made worse by physical exertion Feeling worse for ≥24 hours after exercising	OR= 0.79 (0.67-0.95)* OR= 0.16 (0.03-0.85)* OR= 0.20 (0.04-0.88)*

Table 3.3 (continued)

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Huibers et al[12] (2004) (JOEM) Cohort study	2108 employees from 45 companies scoring >34 on CIS, unexplained fatigue, not on sick leave, changed working hours in past year, or more than 1 job · Netherlands · Mean age: 41 · 25% women · Duration: not presented	4, 8, 12, 16, 20 months, 2 years CIS · Drop-out 37% at T=2 years, 16% at T=8 months · Completers were less fatigued	Fatigue recovery 39% (4 months, 8 months) 40% (1 year) 37% (16 months) 41% (20 months) 40% (2 years) Sickness absence cases 1.8% (4 months) to 3.1% (2 years) no consecutive sickness absence cases	Predictors for recovery during 2 years of FU Fatigue severity (CIS) Work-related exhaustion (MBI) Anxious mood Conflicts with colleagues Self-rated health (SF36) Age*time interaction Need for recovery Supervisor social support (JCQ) Self-rated fatigue complaints Psychological attribution of fatigue complaints	 RR= 0.79 (0.74-0.84)* RR= 0.85 (0.80-0.91)* RR= 0.93 (0.88-0.98)* RR= 0.77 (0.64-0.93)* RR= 1.31 (1.16-1.48)* OR=0.97 (0.94-0.99)* OR=0.89 (0.82-0.96)* OR=0.93 (0.87-0.99)* OR=0.55 (0.41-0.74)* OR=1.19 (1.03-1.37)*
Huibers et al[13] (2004) (JECH) Selection of same cohort study	1143 employees with available data on FU · Mean age: 42 · 28% women · Duration: not presented	44 months · Drop-out: not presented	52%	*Non-fatigue vs. CFS-like fatigue* Fatigue severity (CIS) Exhaustion (MBI) Educational level - low vs high - middle vs high Self-reported GP visit Self-reported OP visit Self rated good health *Non-fatigue vs. non-CFS like fatigue* Fatigue severity (CIS) Self perceived activity (CIS) exhaustion (MBI) anxious mood self rated good health	 OR=0.73 (0.54-0.90)* OR=0.60 (0.46-0.78) * OR=0.38 (0.19-0.79)* OR=0.42 (0.22-0.79)* OR=0.33 (0.18-0.58)* OR=2.17 (1.05-4.55)* OR=1.79 (1.05-3.03)* OR=0.81 (0.73-0.95)* OR=0.85 (0.74-0.96)* OR=0.76 (0.65-0.88)* OR=0.82 (0.71-0.94)* OR=1.56 (1.18-2.08)*

First author; design	Study population	Follow-up measurements; Measurement of fatigue on baseline and outcome	% recovery at follow-up, functional outcome if presented	Prognostic factors	Strength of association (95% CI) with recovery *significant association
Huibers et al[14] (2004) (J Psychosom Res) RCT	151 employees scoring >34 on CIS, fatigued for at least 4 months, on sick leave for 6 or more weeks, unexplained fatigue, no other intervention for fatigue, psychological treatment or sick leave that is not health-related · Netherlands · Mean age: 43 · 55% women · Duration: mean 2.3 years	4, 8, 12 months CIS · Drop-out 9%	Fatigue recovery 34% (4 months) 37% (8 months) 43% (1 year) Work resumption 55% (4 months) 61% (8 months) 62% (1 year)	Predictors for 1-year outcome Psychological attributions Pain (SF-36) Self-rated health (SF-36) Professional efficacy (MBI) Cognitive difficulties (SCL) *Predictors for CFS-like subgroup* Self-efficacy Pain (SF-36) *Predictors for non-CFS like subgroup* Psychological attributions Somatisation	 OR= 1.62 (1.04-2.43)* OR= 0.54 (0.40-0.74)* OR= 1.69 (1.19-2.39)* OR= 0.61 (0.39-0.94)* OR= 0.57 (0.37-0.92)* OR= 2.50 (1.19-5.18)* OR= 0.40 (0.22-0.74)* OR= 1.75 (1.05-3.08)* OR= 0.33 (0.17-0.66)*
Leone et al[15] (2006) same population	· No work incapacity	4 years · Drop-out 16% · Completers less fatigued, higher levels of physical functioning	Fatigue recovery 43% no severe fatigue Full work incapacity 26%	-	-

Table 3.4 Prognostic indicators of recovery

Prognostic factor	Strength of association (95% CI)	Attrition bias; attrition rate
Primary care		
Demographic characteristics		
Age (3 studies)	>64 vs. younger: OR=0.24 (0.08-0.76)[22] Not significant[16,23]	No; 0% dropout
Education (2 studies)	OR (high school or college vs. less than high school) =0.29 (0.10-0.83)[24] Not significant[8]	Yes (completers older); 37% dropout
Race (1 study)	OR (white vs. non-white)=12 (1.47-98.2)[24]	Yes (completers older) ; 37% dropout
Gender (2 studies)	Not significant[16,23]	
Marital status (1 study)	Not significant[8]	
Having children (1 study)	Not significant[8]	
Occupation (1 study)	Not significant[16]	
Income (1 study)	Not significant[8]	
Fatigue		
Severity (1 study)	Number of fatigue symptoms: OR=0.42 (0.25-0.68), 0.52 (0.32-0.85), 0.66 (0.52-0.83) for different fatigue groups[23]	Yes (completers higher GHQ score); 32% dropout
Duration (1 study)	>3 months, OR=0.44 (0.23-0.85)[16]	Yes (completers older); 17% dropout
Health and functioning		
Probability of having mental problems (GHQ) (2 studies)	GHQ-28 (scale not given, interpretation unclear): OR=0.96 (0.93-0.99)[23] Not significant[16]	Yes (completers higher GHQ score); 32% dropout
Previous episodes of anxiety or depression (1 study)	Yes vs. no: OR= 0.32 (0.16-0.65)[16]	Yes (completers older); 17% dropout
Better functioning (1 study)	Sickness Impact Profile (scale not given), score ≤13: OR=3.35 (1.15-9.77)[22]	No; 0% dropout
Anxiety/depression (GHQ and SOFA) (1 study)	scores GHQ>4 and SOFA<3: OR=0.25 (0.12-0.52)[21]	Bias or dropout unknown
Self-reported health (1 study)	Not significant[8]	
Lab results erytrocyte sedimentation rate (ESR) (1 study)	Not significant[22]	
Any chronic physical disorder (1 study)	Not significant[23]	

Prognostic factor	Strength of association (95% CI)	Attrition bias; attrition rate
Community		
Demographic characteristics		
Age (1 study)	'Age*time interaction', interpretation unclear: OR=0.97 (0.94-0.99)[12]	Yes (completers less fatigued); 37% dropout
'Gender and marital status' (1 study)	r^2 =0.04, p<0.05 for outcome *chronic fatigue*[39], unclear which gender shows better prognosis	Bias unknown; 22% dropout
Education (1 study)	OR (lower vs high)=0.38 (0.19-0.79)[13] OR (middle vs high)=0.42 (0.22-0.79)[13]	Bias or dropout n.a.
Fatigue		
Severity (3 studies)	Fatigue Scale (scale 0-33), per point increase: OR= 0.79 (0.67-0.95)[27]	No; dropout n.a.
	CIS (scale 8-56), per SD: RR = 0.79 (0.71-0.84)[12]	Yes (completers less fatigued); 37% dropout
	OR= 0.81 (0.73-0.95) at 44 months[13] OR= 0.73 (0.54-0.90) no fatigue vs. CFS-like fatigue	Bias or dropout n.a.
	Always vs usually fatigued OR=0.34 (0.19-0.60)[26]	Bias unknown; 16% dropout
Aggravating factors: Fatigue worse after physical exertion (1 study)	Yes vs. no: OR=0.16 (0.029-0.85)[27]	No; dropout n.a.
Feeling worse for ≥ 24 hours or more after exercising (1 study)	Yes vs. no: OR=0.20 (0.044-0.88)[27]	No; dropout n.a.
Need for recovery (1 study)	Need for Recovery scale (range not given), Indicating short-term effects of day of work; per SD: OR=0.89 (0.82-0.96)[12]	Yes (completers less fatigued); 37% dropout
Self-rated fatigue complaints (1 study)	Yes=1: OR=0.55 (0.41-0.74)[12] (interpretation unclear)	Yes (completers less fatigued); 37% dropout
Exhaustion (1 study)	Maslach Burnout Inventory-General Survey, (higher score indicates higher level): RR=0.85 (0.80-0.91)[12]	Yes (completers less fatigued); 37% dropout
	OR= 0.60 (0.46-0.78) at 44 months[13], OR= 0.76 (0.65-0.88) no fatigue vs. CFS-like fatigue	Bias or dropout n.a.
Health and functioning		
Self-rated health (2 studies)	SF-36 (good=1): RR=1.31 (1.16-1.48)[13]	Yes (completers less fatigued); 37% dropout
	OR= 1.56 (1.18-2.08) at 44 months[14] OR= 1.79 (1.05-3.03) no fatigue vs. CFS-like fatigue	Bias or dropout n.a.
	SF-36 (scale 0-100), per SD: OR=1.69 (1.19-2.39)[14]	Bias unknown; 9% dropout
Being bothered by long term health problems (1 study)	Yes vs. no long term health problems: OR=0.49 (0.32-0.77)[26]	No; 16% dropout
Pain (1 study)	SF-36 (scale 0-100), more pain per SD: OR=0.54 (0.40-0.74)[14]	Bias unknown; 9% dropout
Somatisation (1 study)	SCL-90 (scale not given) higher score: OR=0.33 (0.17-0.66)[14]	Bias unknown; 9% dropout

Table 3.4 (continued)

Prognostic factor	Strength of association (95% CI)	Attrition bias; attrition rate
Self-perceived activity (1 study)	CIS (scale 3-21), per SD: OR=0.85 (0.74-0.96)[12]	Bias or dropout n.a.
Anxious mood (1 study)	Added scores on 3 items of anxiety, higher score indicates higher level of anxious mood; per SD: RR=0.93 (0.88-0.98)[12] OR= 0.82 (0.71-0.94) at 44 months[13]	Yes (completers less fatigued); 37% dropout[12] Bias or dropout n.a.[13]
Probability of having mental problems (1 study)	GHQ-12 (scale not given), higher score: r^2=0.11 (p<0.001)[39] for outcome *chronic fatigue*	Bias unknown; 22% dropout
Cognitions		
Psychological attributions (3 studies)	Yes vs. no: OR= 1.19 (1.03-1.37)[12]	Yes (completers less fatigued); 37% dropout
	Modified Causal Attribution List, Yes vs. no: OR= 1.62 (1.04-2.43)[14]	Bias unknown; 9% dropout
	Psychological or ME attribution for outcome chronic fatigue: r^2= 0.15 (p<0.001)[39] (attributions are associated with more fatigue)	Bias unknown; 22% dropout
Self-efficacy (1 study)	CFS-like subgroup: Self-efficacy scale (SES) (higher score indicates higher level of self-efficacy) OR=2.50 (1.19-5.18)[14]	Bias unknown; 9% dropout
Cognitive difficulties (1 study)	SCL-90 (scale not given, interpretation unclear): OR=0.57 (0.37-0.92)[14]	Bias unknown; 9% dropout
Health care		
Self-reported GP visit (1 study)	Yes vs. no: OR=0.33 (0.18-0.58)[13]	Bias or dropout n.a.
Self-reported visit to occupational physician (1 study)	Yes vs. no: OR=2.17 (1.05-4.55)[13]	
Work characteristics		
Positive challenges in job (1 study)	General Nordic Questionnaire for Psychological and Social factors at Work (scale 1-5) medium level of quintiles: OR=2.16 (1.27-3.69)[26]	No; 16% dropout
Support from supervisor (2 studies)	General Nordic Questionnaire for Psychological and Social factors at Work (scale 1-5) medium level of support): OR=0.45 (0.24-0.85)[26]	No; 16% dropout
	JCQ (higher scores indicates higher level) OR=0.93 (0.87-0.99)[12]	Yes (completers less fatigued); 37% dropout
Feedback about quality of work (1 study)	General Nordic Questionnaire for Psychological and Social factors at Work (scale 1-5) (rather seldom) OR= 1.96 (1.19-3.22)[26]	No; 16% dropout
Professional efficacy (1 study)	Maslach Burnout Inventory-General Survey (higher scores indicate higher levels of (perceived) efficacy): OR=0.61 (0.39-0.94)[14]	Bias unknown; 9% dropout
Conflicts with colleagues (1 study)	Yes vs no: RR=0.77 (0.64-0.93)[12]	Yes (completers less fatigued); 37% dropout

n.a. = not applicable.

Three demographic characteristics (age, gender, education) were investigated in more than one study. Older age was significantly associated with poor outcome in one of four studies; this was a relatively small population without attrition bias but with a higher mean age than other studies.[22] Gender was assessed in two studies but not significantly associated with outcome.[16,23] Three studies reported on education as a prognostic factor. In two large cohorts higher education was positively associated with recovery[13,23], but the association was significant in only one.[13] In another smaller study, higher education was significantly associated with poor outcome.[24] All studies showed attrition bias or lacked information on selective loss to follow-up.

Mental health was measured in a variety of ways. Most studies reported significant associations between a measure of poor mental health (anxiety or depression, a previous episode of anxiety or depression, anxious mood, somatisation or probability of having mental problems) and lower probability (odds) of recovery from fatigue (ORs=0.25-0.94). However, all studies either lacked information on attrition, or showed attrition bias, sometimes specifically for this variable (GHQ score).[23] In one study, in which insufficient data were presented to compute ORs, anxiety or depression were not significantly associated with poor outcome, but more depressed patients were lost to follow-up.[19] Self-reported good health was significantly associated with recovery in two out of three studies[12-14], however one of these reported selective drop-out of more fatigued participants. Attributing fatigue to psychological factors showed significant associations with recovery in these same studies; in another study the prognostic value of attributions was unclear.[39]

Discussion

Main results

In primary care, only four out of ten studies included a population of patients visiting their GP for fatigue. Recovery rates differed widely in studies concerning primary care attenders, whereas studies among patients presenting with fatigue and in the community showed a recovery rate ranging from 35 to 55%. Most studies with lowest recovery rates (22-23%) had small sample sizes. Four studies, of which only one was conducted in primary care, reported a reasonable sample size and showed no evidence of attrition bias. Improvement or recovery in these studies varied from 11 to 55%. Virtually all studies included a majority of participants with chronic fatigue at baseline. The results of this review show that in primary care very few studies have been conducted with a reasonable sample size and evidence of minimal loss or selective follow-up.

In primary care studies, follow-up was mostly limited to one measurement at one year after baseline assessment. Consequently, it remains unclear whether the course of fatigue shows fluctuations. Included community studies generally had a longer follow-up, but again mostly without repeated measurements of fatigue.

Only three of the studies presented any functional outcome, and only one of these reported on physical functioning. However, as we did not specifically search for studies reporting on functional outcomes in fatigued persons, we might have missed studies in which functioning was presented as the main or only outcome. Even so, in the studies we did identify, a longitudinal analysis, which would provide information on the temporal relation between fatigue and functioning, was not performed.

Prognostic factors were presented in half of the included studies. Although many potential predictors of the course of fatigue were investigated, few factors were assessed in several studies. Severity of fatigue was the only prognostic factor which fulfilled our criterion of 'sufficient evidence'. Factors lacking sufficient evidence because of attrition bias, but showing consistent and significant associations with outcome in at least two studies of reasonable sample size were self-reported health, mental health and psychological attributions of fatigue.

Comparison with the literature

Joyce et al included primary care studies in their review, but similar to this review, in most populations the mean duration of fatigue at baseline was already longer than six months and may be considered chronic.[6] They reported a higher overall percentage of recovery, based however on small and partly selected post-viral populations. Regarding prognostic factors, studies on chronic fatigue (syndrome) in secondary care showed similar associations between poor fatigue outcome and a longer duration of fatigue at baseline, somatic attributions, anxiety and depression or mental distress.[5,28-34] As for level of education, we did not find consistent evidence for its prognostic value. In a national survey in primary care presenting cross-sectional associations, fatigue when presented to the GP was associated with higher education and poor psychological health. Also, self-rated poor health was associated with fatigue, consistent with the finding of more somatic comorbidity and more symptoms in fatigued patients.[2] Other factors which we did not find in our review, but have been reported to be associated mainly cross-sectionally with levels of fatigue include physical exercise[35,36], sleep quality, care for young children and dietary habits.[2]

Strengths and limitations

In this systematic review, we used an extensive search strategy to identify all relevant studies, and performed a methodological assessment of selected studies. Previous

reviews on fatigue lack an assessment of methodological quality, which is essential when pursuing an objective evaluation of the results, that can take into account the potential influence of bias.

We did not use a total score for assessing methodological quality, since any cut-off point would be arbitrary and would ignore the heterogeneity of assessed methodological criteria. Rather, we preferred to compare studies reporting on similar prognostic factors or outcomes more specifically on those criteria that discriminated between the methodological quality of included studies, in this case attrition bias.

We found considerable variability in study populations. Half of the studies included patients with unexplained fatigue. In community studies, populations of employees had proportions of women varying between 25 and 96%. In primary care, some of the studies reported on patients presenting with fatigue while others reported on all primary care attenders. The heterogeneity of studies did not allow a meta-analysis of the course of fatigue or predictors of recovery, which would have facilitated analysing the influence of quality indicators. Evaluating scores from all studies however revealed some overall similarities and major deficits in methodological quality. In almost all studies, response rate and selectivity of response were unknown, and in most studies there was a (possible) selective loss-to-follow-up.

In primary care studies, diagnoses are a relevant outcome, which could account for poor prognosis. We did not extract data on diagnostic outcomes. However, since many studies included populations with medically unexplained fatigue, results would be limited in this respect. Yet, co-existing somatic health problems could also influence the course of fatigue. This prognostic factor was assessed in only one study in our review, and the results showed no significant association with the outcome of fatigue.[23]

Recommendations for research

In view of the results of this review, we have some suggestions for a more ideal design of prognostic studies on fatigue. To allow a better estimate of outcome, prognostic studies should have a sufficient sample size and assess the potential prognostic value of biological, psychological and social factors. For the same reason, studies should present response and attrition rates of fatigued participants, and possible selectivity of response and follow-up. Furthermore, different factors may influence prognosis in patients with either new onset or alreadychronic fatigue. Only two studies in our review reported on duration as a prognostic factor, which appeared to be associated with poor outcome. Most of the studies which presented baseline duration of fatigue included chronically fatigued populations. In order to determine which fatigued patients will *develop* a chronic course of their symptoms, it is necessary to restrict inclusion to persons with a

maximum rather than a minimum duration of fatigue. Furthermore, to better investigate trajectories of fatigue, including recurrences, repeated assessments should be performed.

Recommendations for the GP

Which characteristics of patients may predict a poor short-term prognosis cannot be concluded from our review. Regarding long-term prognosis, we did not find much evidence for factors other than baseline severity of fatigue. We found limited evidence for a longer duration of fatigue, anxiety and depressive symptoms to predict a poor outcome of fatigue, whereas psychological attributions and self-rated good health may predict a positive outcome.

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Appendix: Explanation of the criteria in Table 3.1

A.	Positive if criteria for in/exclusion are provided; and the baseline sample is adequately described for key characteristics (sex, age)
B.	Positive if baseline fatigue was measured using structured, validated instruments
C.	Positive if recruitment is described, possibly including time period of recruitment and geographic location of recruitment
D.	Positive if the sample is representative: selection of subjects should be consecutive or random
E.	Positive if response rate of eligible participants on baseline measurement > 75%
F.	Positive if there was no selective response; negative if there was a selective response; ? if no information was presented about patient/symptom characteristics of responders and non-responders
G.	Positive if number of drop-outs on at least one measurement during follow-up (i.e. main outcome measures) is < 20%
H.	Positive if there was no selective loss-to-followup; negative if there was selective loss-to-followup; ? if no information was presented about important patient/symptom characteristics of completers and non-completers
I.	Positive if the follow-up period was at least 3 months
J.	Positive if measurements used for fatigue outcome were the same as those for baseline
K.	Positive if prognostic factors (other than fatigue) were measured in a standardised way
L.	Positive if frequency was reported for fatigue outcome measures
M.	Positive if frequency was reported for baseline values of prognostic factors
N.	Positive if univariate or multivariate estimates were provided or could be calculated for the association of a prognostic factor with outcome

4

Prognosis of fatigue and functioning in primary care: a one-year follow-up study

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Abstract

Purpose

Although fatigue is a common presenting symptom in primary care and its course and outcomes often remain unclear, cohort studies among patients seeking care for fatigue are scarce. We therefore aimed to investigate patterns in the course of fatigue and relevant secondary outcomes in a large cohort of patients who sought care for a main symptom of fatigue.

Methods

We performed an observational cohort study in 147 primary care practices. Patients consulting their general practitioner for a new episode of fatigue were sent questionnaires at 1, 4, 8, and 12 months after baseline. We collected measures of fatigue, perceived health and functioning, absenteeism, psychological symptoms, and sleep using the Checklist Individual Strength, the 36-Item Short Form Health Survey, the Four-Dimensional Symptoms Questionnaire, and the Pittsburgh Sleep Quality Index. Patients were classified into 4 subgroups based on fatigue severity scores over time. We assessed patterns in the course of all outcomes in these subgroups and in the total population, and tested changes over time and differences between subgroups.

Results

A total of 642 patients were enrolled in the study. Response rates during follow-up ranged between 82% and 88%. For 75% of the patients, 4 distinct groups could be discerned: 26% of patients had continuously high scores for fatigue, 17% had a fast recovery, 25% had a slow recovery, and 32% initially improved but then had a recurrence of fatigue. Patterns for the secondary outcomes of symptoms and functioning were all similar to the pattern for fatigue within each of the subgroups.

Conclusions

The findings of this study suggest a longitudinal relationship between the severity of fatigue, impaired functioning, psychological symptoms, and poor sleep. Physicians should be aware that a substantial proportion of patients seeking care for fatigue have these additional health and psychosocial problems.

Introduction

Fatigue is a nonspecific symptom and often the main one for which patients consult general practitioners; its prevalence ranges from 5% to 10%.[1-4] Fatigue frequently remains the only (symptom) diagnosis in an episode of care.[2] Serious functional impairment, psychological symptoms, and disturbed sleep often accompany fatigue.[5-8] Knowledge about the course of fatigue and related problems in a heterogeneous primary care population is scarce, however, because most longitudinal studies on fatigued populations have been performed in highly selected groups, such as patients with chronic fatigue syndrome (CFS), postviral fatigue, or cancer.

Available studies on fatigue in primary care often concern a general population of primary care patients rather than patients seeking care for fatigue as a main symptom, have a follow-up limited to a single measurement rather than repeated measurements, or have a small sample size. Often, only patients with chronic fatigue have been included.[9] We therefore investigated the course of fatigue in a large cohort of patients seeking care for a main symptom of fatigue using repeated measurements over a period of 1 year.

Additionally, as outcomes in available studies have been limited mainly to measures of fatigue, we assessed relevant secondary measures of daily functioning, work absence, psychological symptoms, and sleep. Our second aim was to examine whether the course of these secondary outcomes has a pattern similar to that of the fatigue itself.

Methods

Design and recruitment

The target population of our observational cohort study included adult patients who sought care for a main symptom of fatigue in Dutch primary care. We approached all general practitioners in several geographic areas, including rural and urban practices, and solo practitioners as well as group practices. From June 2004 to January 2006, 111 general practitioners and 57 trainees from 147 practices total recruited patients with a new episode of fatigue, meaning that the patient had not visited their physician for the same episode of fatigue at any time or for a different episode within the past 6 months. We excluded patients who were receiving or had received chemotherapy or radiotherapy in the preceding 3 months and women who were pregnant or less than 3 months post-partum. Eligible patients were informed about the study by their general practitioner and invited to participate. If the patients were interested, they were sent an

information letter and the baseline questionnaire. Patients were enrolled when they returned a signed consent form. The participating patients completed questionnaires shortly after the consultation (baseline) and at 1, 4, 8, and 12 months after baseline. The study was approved by the Medical Ethical Committee of the VU University Medical Centre, Amsterdam.

Outcome measures

Our primary outcome was fatigue. We measured the severity of fatigue at all time points with the Checklist Individual Strength (CIS), a 20-item questionnaire that has been validated in several fatigued populations.[10] Items are scored on a 7-point Likert scale. A score of 34 or higher on the 8-item subscale of subjective fatigue has been used as a cutoff for severe fatigue.[11,12]

We assessed a variety of secondary outcomes. General health and functioning were measured at all time points with the 36-Item Short-Form Health Survey (SF-36), which includes subscales on physical functioning, physical role functioning, emotional role functioning, social functioning, bodily pain, mental health, vitality, and general health. The Dutch version has been validated in populations with various chronic diseases.[13] Scores on all subscales range from 0 to 100, with higher scores indicating better functioning or health, or less pain. We measured absence from work or refraining from other activities during the past month due to the fatigue with a single question having response options of 0 days, 1 to 5 days, 6 to 10 days, 11 to 20 days, and greater than 20 days. In the descriptive analysis, answers were dichotomized into 0 days vs 1 or more days.

We measured psychological symptoms at baseline and after 1 year with the Four-Dimensional Symptoms Questionnaire (4DSQ). This scale has been validated in primary care populations and discerns levels of distress (16 items), somatization (16 items), depression (6 items), and anxiety (12 items).[14] Scales for individual items range from 0 to 32 for distress and somatization, 0 to 12 for depression, and 0 to 24 for anxiety, with higher scores indicating more frequent psychological symptoms.

We measured sleep problems at baseline and after 12 months with the sleep subscale of the Symptom Checklist 90 (SCL-90), for which normative scores for the general population exist.[15] This scale is scored on a 5-point Likert scale, with a total range of 3 to 15. Additionally, sleep quality was measured more extensively at the 1-month follow-up with the Pitts-burgh Sleep Quality Index (PSQI) in those patients scoring above average on the SCL-90 subscale at baseline. The PSQI is a 19-item checklist validated in patients with depression and patients with sleep disorders. The list is used to evaluate general sleep quality and quantity, yielding a global score (range, 0–21) and 7 component scores.[16] For both sleep scales, higher scores indicate poorer sleep.

Statistical analysis
We used descriptive statistics to analyze the course of fatigue and secondary outcomes over the 12-month follow-up in the total study population. On the basis of the CIS severity score, we defined 4 subgroups of patients with a different course of fatigue over time: a chronic fatigue group having high scores on the CIS (>34) at all time points; a fast recovery group having low scores (≤34) at all follow-up measurements; a slow recovery group having low scores (≤34) after 4, 8, or 12 months; and a recurrent fatigue group having a recurrence of high fatigue scores after initial improvement. We assessed the course of fatigue and of the secondary outcomes over time for each of these 4 subgroups. To test the significance of changes in sleep and psychological symptom scores on the SCL-90 between baseline and 12 months, we performed dependent (paired) *t* tests and used analysis of variance to test differences in these measures between the 4 subgroups at baseline and after 12 months.

Changes over time in mean fatigue score in the total group were analyzed using multivariate analysis of variance (MANOVA) for repeated measures. To test changes over time and differences in the course of outcomes between the 4 fatigue subgroups, we used MANOVA for the continuous SF-36 outcomes and generalized estimating equations (GEE) for the dichotomous outcomes of refraining from daily activities. To assess whether differences between groups in fatigue and other measures were mainly explained by differences at baseline, analyses were also adjusted for baseline levels of outcome measures. For all analyses, we used an α of 0.05 to define statistical significance.

Results

Recruitment and response
The general practitioners invited 856 patients to participate in the study, of whom 642 (75%) consented to participate. Compared with nonparticipants, participants were on average 5 years older ($P<0.01$) and more often female (73% vs 65%; $P<0.05$). The number of patients remaining during follow-up was 562 (88%) at 1 and 4 months, 524 (82%) at 8 months, and 568 (88%) at 12 months.

Participating patients who did and did not subsequently complete any questionnaires did not differ significantly regarding sex or severity of fatigue at baseline; however, patients who completed the 4-, 8-, and 12-month questionnaires were on average 8 years older than the patients lost to follow-up ($P<0.001$). Twenty-four patients completed only the baseline questionnaire, leaving 618 with at least 1 follow-up measurement. The baseline characteristics of the 642 participating patients are presented in Table 4.1. The population was middle-aged and predominantly female and employed. The

majority had been fatigued for more than 6 months before seeking care (58%) and had previously experienced an episode of fatigue (65%). Only small proportions had tried any treatment for their current fatigue.

Fatigue

The time course of fatigue is shown in Table 4.2. At baseline, 90% of all patients scored higher than 34 on the CIS severity scale, indicating that they were severely fatigued. Scores decreased significantly between all successive time points, but the decrease was greatest between baseline and 1 month.

Table 4.1 Self-reported patient characteristics at baseline (n=642)

Patient characteristics	Number of patients	%
Socio-demographic factors		
Age (mean, SD)	41.8 (16.3)	
Gender (female)	467	73
Married or living together	411	64
Care for children	242	38
Paid work	492	77
Educational level		
Primary	40	6
Secondary	483	75
College/university	118	18
Characteristics of fatigue		
Duration (months)		
< 1 month	44	7
1-3 months	98	16
3-6 months	115	19
6-12 months	114	18
≥ 1 year	252	40
Previous episode of fatigue		
No	223	35
Yes, duration < 6 months	246	38
Yes, duration ≥ 6 months	171	27
Treatment for fatigue		
Medication*	52	8.1
Psychologist or social work	26	4.0
Physio- or manual therapy	21	3.3
Diet	9	1.4
Alternative or complementary	31	4.8
Other treatment or care	21	3.3

*Various supplements (e.g. vitamins, iron) (16), benzodiazepines (7), anti-depressants (5), thyroid hormones (4), pain medication (5), other medication for other indications (10), missing or not clear (7)

Because of missing values at 1 or more time points, 136 (22%) of 618 patients with follow-up data could not be classified into any of the 4 subgroups. Of the remaining 482 patients, 123 (26%) fell into the chronic fatigue subgroup, 83 (17%) patients fell into the fast recovery subgroup, 122 (25%) fell into the slow recovery subgroup, and 154 (32%) fell into the subgroup with recurrent fatigue. Patients who could not be classified into 1 of the groups did not differ regarding sex, baseline severity of fatigue, or baseline levels of other outcomes, but were on average 8 years younger (95% CI, –11 to –4.9) and slightly more often reported absence from work at baseline (44% vs 35% among those who could be classified; Pearson χ^2, $P<0.05$).

Table 4.2 Time course of fatigue and other symptoms in the study population

Outcome measure [reference population score][a]	Baseline n=642	1 month n=562	4 months n=562	8 months n=524	12 months n=568
Fatigue (CIS)					
Severity score (mean, SD) [17]	46 (8.4)	38 (11)	35 (12)	34 (13)	32 (14)
Score >34, n (%) (range, 8-56)	578 (90%)	369 (66%)	324 (57%)	257 (49%)	259 (46%)
Total score (mean, SD) [42] (range, 20-140)	96 (20)	84 (24)	78 (26)	75 (28)	71 (28)
Health status (SF-36) (mean, SD)					
Physical functioning [83]	74 (23)	78 (22)	81 (20)	82 (20)	83 (20)
Physical role functioning [76]	35 (36)	51 (40)	59 (40)	62 (40)	66 (40)
Emotional role functioning [82]	64 (41)	72 (39)	75 (37)	76 (38)	77 (37)
Social functioning [84]	60 (22)	68 (22)	71 (23)	73 (22)	76 (23)
Bodily pain [75]	72 (24)	77 (24)	78 (24)	78 (25)	79 (24)
Mental health [77]	63 (18)	68 (18)	68 (18)	69 (18)	71 (18)
Vitality [69]	36 (16)	46 (18)	50 (19)	53 (21)	56 (21)
General health [71]	60 (19)	60 (20)	61 (19)	62 (21)	63 (21)
Absence from work[b] (n)	238 (38%)	184 (33%)	138 (25%)	118 (23%)	109 (20%)
Refraining from other activities[b] (n)	352 (56%)	281 (50%)	219 (40%)	212 (41%)	205 (38%)
Psychological symptoms (4DSQ) mean (SD); % elevated[c]					
Distress	13 (7.4); 61%				8.7 (7.0); 35%
Somatisation	11 (6.2); 48%				7.9 (6.1); 30%
Depression	1.7 (2.6); 24%				1.0 (2.1); 15%
Anxiety	2.5 (3.6); 10%				1.7 (3.1); 5%
Sleep (SCL-90); mean (SD); % above average[d]	7.0 (3.1); 65%				6.4 (2.7); 58%

4DSQ=Four-dimensional Symptom Questionnaire; SF-36=36-item Short-Form Health Survey; SCL-90=Symptom Checklist-90. [a]Reference scores based on 53 healthy subjects for the CIS[10], and a random sample of 1742 people from the general population for the SF36[17]. [b]Percentages based on available data for each time point. [c]On the 4DSQ, scores are elevated if they exceed 10 for distress, 2 for depression, 7 for anxiety, and 10 for somatization. [d]On the sleep scale of the SCL-90, scores are elevated if they exceed 5 for women and 4 for men.

Figure 4.1 shows the mean scores of fatigue severity for the 4 subgroups having a different course of fatigue. The subgroups had distinct patterns of fatigue severity that differed significantly, both before and after adjustment for the severity of fatigue at baseline. On closer inspection, the duration of fatigue already differed at baseline; the proportions of patients with chronic fatigue (duration >6 months) at presentation ranged from 68% in the chronic fatigue group to 37% in the fast recovery group (Pearson χ^2, $P<0.001$).

Perceived health and functioning

Changes in perceived health over time, assessed with the SF-36, were significant for all subscales (MANOVA, $P<0.001$) (Table 4.2). Apart from vitality, baseline mean scores were particularly low for physical role functioning, social functioning, and emotional role functioning compared with the scores in a Dutch reference population.[17] These areas, however, were also the areas showing the largest improvement over the year. Changes over time across the 4 subgroups for all SF-36 scales had a pattern similar to that of fatigue, with the most distinct differences evident between the chronic fatigue and fast recovery subgroups, as exemplified in Figure 4.2a. Differences were also significant ($P<0.001$) on all subscales after adjustment for baseline scores.

Missed work or other activities

As shown in Table 4.2, a considerable proportion of patients reported that they were absent from work or refrained from other activities at least 1 day in the past month because of their fatigue. Figures 4.2 b and 2c show the proportion of patients reporting these outcomes by subgroup. The patterns were in part similar to those for severity of fatigue and the SF-36 scores, with these outcomes more often reported in the chronic fatigue subgroup during the entire year of follow-up and least often reported in the fast recovery group. The (more heterogeneous) groups with slow recovery or a recurrent course of fatigue also had more work absence in the first months after consulting the general practitioner. Most of these absences, however, were of relatively short duration (1–5 days). Differences over time between subgroups were significant (GEE analyses, $P<0.001$) for both outcomes (absence from work and refraining from other activities), before and after adjustment for differences in baseline values.

Psychological symptoms

Whereas a minority of patients had symptoms of depression or anxiety, a substantial proportion had elevated scores on the 4DSQ distress and somatization scales at baseline, and one-third still had elevated scores after 1 year (Table 4.2). Mean scores on all scales had decreased significantly from baseline after 12 months ($P<0.01$).

Figure 4.1 Course of the severity of fatigue in the four subgroups
(Checklist individual strength)

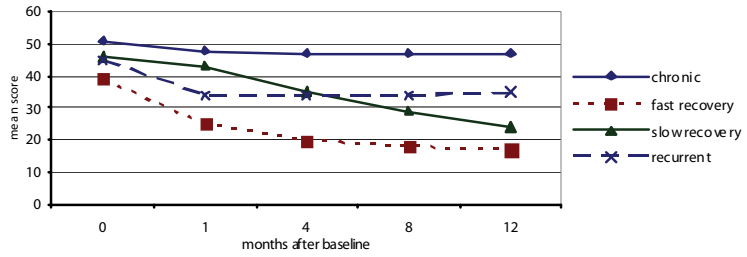
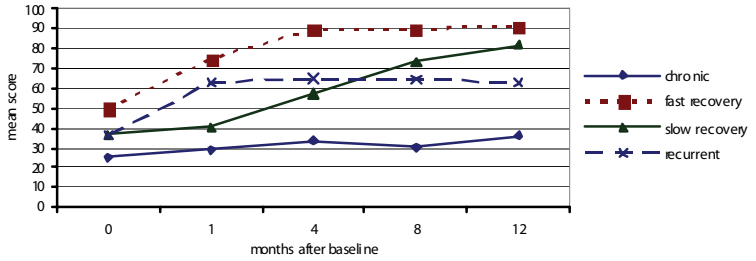
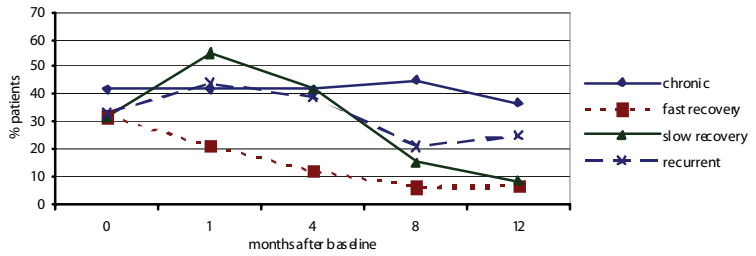


Figure 4.2 Course of functional outcomes in the four subgroups

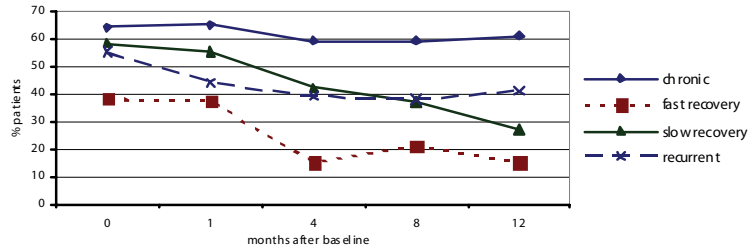
a. Physical role functioning (SF-36)



b. Absence from work



c. Refraining from other activities



Among the 4 subgroups, differences in the change in psychological symptoms were significant for distress and somatization ($P<0.001$), but not for depression ($P=0.34$) and anxiety ($P=0.19$) (Table 4.3). Mean changes between baseline and the 12-month follow-up were largest in patients having a fast or slow recovery in terms of fatigue severity. Changes over time were small and not significant for depression and anxiety in the chronic fatigue subgroup.

Table 4.3 Mean scores for psychological symptoms (4-DSQ) and sleep (SCL-90) in the four subgroups at baseline and after 12 months

Measure by subgroup	Baseline: mean (SD)	Elevated score[a]: n (%)	12 months: mean (SD)	Elevated score: n (%)	Mean change (95% CI)
Distress					
Chronic course	15.8 (7.3)	93 (76%)	13.1 (7.7)	70 (58%)	2.6 (1.4-3.9)
Fast recovery	9.5 (6.4)	33 (40%)	3.7 (3.9)	6 (7%)	5.8 (4.5-7.2)
Slow recovery	13.8 (7.3)	78 (64%)	7.3 (5.6)	31 (26%)	6.5 (5.3-7.7)
Recurrent fatigue	12.7 (6.9)	90 (59%)	9.1 (6.2)	56 (38%)	3.6 (2.5-4.8)
Somatisation					
Chronic course	13.6 (6.9)	79 (64%)	11.6 (6.6)	68 (57%)	2.1 (1.1-3.0)
Fast recovery	8.1 (5.0)	21 (25%)	3.8 (3.6)	4 (5%)	4.3 (3.3-5.2)
Slow recovery	11.2 (5.4)	63 (52%)	6.7 (5.4)	21 (17%)	4.5 (3.7-5.4)
Recurrent fatigue	10.5 (5.6)	67 (44%)	7.9 (5.3)	43 (29%)	2.6 (1.7-3.4)
Depression					
Chronic course	2.6 (3.2)	46 (37%)	2.2 (3.0)	43 (36%)	0.4 (-0.1-0.9)[b]
Fast recovery	1.0 (2.1)	13 (16%)	0.1 (0.5)	1 (1%)	0.8 (0.4-1.3)
Slow recovery	1.4 (2.2)	28 (23%)	0.5 (1.3)	8 (7%)	0.8 (0.5-1.2)
Rrecurrent fatigue	1.3 (2.0)	29 (19%)	0.8 (2.0)	16 (11%)	0.5 (0.2-0.8)
Anxiety					
Chronic course	3.4 (4.3)	20 (16%)	2.9 (3.9)	13 (11%)	0.5 (-0.1-1.2)[b]
Fast recovery	1.1 (1.9)	2 (2%)	0.4 (1.0)	0	0.7 (0.3-1.0)
Slow recovery	2.6 (3.4)	13 (11%)	1.4 (2.3)	4 (3%)	1.2 (0.7-1.7)
Recurrent fatigue	2.3 (3.5)	15 (10%)	1.8 (3.4)	8 (5%)	0.5 (0.0-1.0)
Sleep					
Chronic course	7.4 (3.4)	80 (66%)	7.5 (3.1)	90 (73%)	0.2 (-0.6-0.3)[b]
Fast recovery	6.0 (2.8)	43 (52%)	5.1 (2.1)	36 (43%)	0.9 (0.2-1.5)
Slow recovery	7.7 (3.3)	91 (75%)	6.2 (2.4)	67 (55%)	1.5 (1.0-2.0)
Recurrent fatigue	6.7 (3.0)	96 (62%)	6.5 (2.6)	91 (59%)	0.3 (-0.2-0.7)[b]

4DSQ=Four-dimensional Symptom Questionnaire; SCL-90=Symptom Checklist-90; CI=confidence interval. Note: 123 patients had a chronic course, 83 had a fast recovery, 122 had a slow recovery, and 154 had recurrent fatigue. [a]Cutoffs for elevation of 4DSQ scores and SCL90 scores are as indicated in Table 4.2. [b]Not significant.

Sleep

Two-thirds of all patients scored above average on the SCL-90 sleep scale at baseline (Table 4.2) and were asked to complete the PSQI after 1 month (response rate, 86%; n=359). Results on the PSQI showed that these patients had high scores for sleep latency (time awake before sleeping), daytime dysfunction, sleep disturbances, and subjective

sleep quality; nevertheless, 63% of this group said they slept "reasonably well" (Table 4.4). One-third of the cohort had global scores of 5 or higher, however, indicating that they had poor overall quality of sleep. Most patients reported that they slept more than 6 hours per night. Differences between subgroups were significant for each domain of the PSQI and again most pronounced between the chronic fatigue and fast recovery subgroups. After 12 months, SCL-90 sleep scores, which differed between subgroups both at baseline and after 12 months ($P<0.001$) improved but were still above average in 58% of all patients (Table 4.2).

Table 4.4 Sleep (PSQI scores) at one month after baseline, for total study population and by subgroup

Measure	Total (n=359)	Chronic course	Fast recovery	Slow recovery	Recurrent fatigue	P-value[a]
PSQI score						
Total, mean (SD)	7.23 (3.55)	9.17 (3.96)	4.60 (2.19)	7.53 (3.23)	6.48 (3.15)	<0.001
N (%) with score >5	229 (62)	64 (82)	9 (21)	63 (70)	50 (55)	
Sleep quality						
Reasonably well, %	63	53	82	57	70	<0.001[b]
Very well, %	5.5	3.8	11	5.6	4.4	
Time awake before sleeping						
Mean (SD), minutes	30 (31)	36 (38)	18 (14)	31 (30)	26 (24)	<0.01
>30 minutes, %	26	37	9.3	27	19	
Sleep duration						
Mean (SD), hours	7.10 (1.34)	6.64 (1.36)	7.33 (1.03)	7.15 (1.41)	7.18 (1.22)	<0.05
>6 hours, %	88	75	98	89	90	
Sleep efficiency						
Mean (SD), %	84 (16)	78 (16)	89 (10)	84 (16)	85 (18)	<0.01
>85%, %	53	41	67	48	54	
Use sleep medication, %	20	29	4.5	22	19	<0.05

PSQI=Pittsburgh Sleep Quality Index. Note: to enable a more straightforward interpretation, component scores are not presented. [a]For difference between groups, determined by analysis of variance. [b]For well (reasonably well and very well) vs bad. [c]Sleep time as percentage of total bedtime.

Discussion

In this cohort of primary care patients consulting general practitioners because of fatigue, the proportion of patients who were severely fatigued decreased from 90% to 46% over 1 year. Among patients with complete follow-up, we identified 4 subgroups that had distinctly different courses of fatigue. Patterns in these subgroups showed that a reduction in severity of fatigue over time was associated with improvements in functioning, sleep, and psychological symptoms.

Fatigue

The proportion of patients showing improvement during the year is in line with previous studies of smaller cohorts of patients seeking care for fatigue.[3,18,19] Strikingly, a majority of patients were already chronically or recurrently fatigued when they visited the general practitioner, and most reported severe fatigue. Our study is the first to use the CIS in primary care, and compared with other populations, our patients had mean scores at baseline that were close to those of patients with CFS or multiple sclerosis.[10] Because we recruited patients when they were seeking care for their fatigue, the fatigue may have been relatively severe at presentation. The improvement of symptoms after consultation may therefore partly represent regression to the "mean level of fatigue" after the visit or the self-limiting course of fatigue, or may be the result of effective care by the general practitioner.

Functioning

Patients in this study often had impairment due to fatigue, as was evident from both their low levels of role functioning and the substantial proportions who missed work or other daily activities because of their fatigue. Baseline SF-36 scores were comparable to those recently found among primary care patients who had a main symptom of unexplained fatigue.[20] The impact of fatigue on perceived health and functioning was not as strong as that reported for patients with CFS; scores for pain, general health, and physical functioning were closer to those for the general population than those for CFS patients.[17,21] In the group with persistent fatigue, most SF-36 scores were in between those of the total population and those of CFS patients.

Psychological symptoms

The co-occurrence of fatigue and psychological symptoms has been reported extensively in various populations including primary care patients, the general population, and employees.[22-28] In our cohort study, all 4 subgroups had a similar pattern of psychological symptom scores, with more patients reporting symptoms of distress and somatization and fewer scoring above the threshold for depression or anxiety. Patients with a chronic course of fatigue had mean 4DSQ scores that were comparable to those of primary care patients seeking care for psychosocial problems[14], although our population had somewhat lower anxiety scores. This finding demonstrates the severity of psychological problems in patients with chronic fatigue. In the total population, mean scores after 1 year were similar to those in a random sample of general practitioner consulters.[14] The association between the number of experienced somatic symptoms and psychiatric comorbidity has been reported before.[27,29] Our findings could reflect several processes, such as physical expression of psychological symptoms, or a heightened awareness of physical symptoms.[30-32] These processes are difficult to measure in large, epidemiologic studies. It should be noted that existing somatization

scales, such as the one we used, represent only the number of experienced symptoms; therefore, we cannot ascertain the origin of these symptoms or patients' perceptions of the symptoms.

Sleep

To our knowledge, this is the first time that sleep quality has been measured in fatigued primary care patients. The different patterns we found in our subgroups indicate that sleep quality deserves attention in patients visiting the general practitioner for fatigue. Sleep scores in the chronic fatigue subgroup were generally similar to those reported for depressed patients.[16,33,34] In our fatigued population, sleep quality was more of a problem than sleep duration. This finding corresponds to observed PSQI patterns in patients with CFS[35] and to the results of a population-based study, in which fatigue was predicted by sleep quality and psychological symptoms rather than by amount of sleep.[5] Both in populations reporting vital exhaustion and in populations reporting major stress or depression, a poorer quality of sleep has been reported by patients who show a reduction of slow wave sleep, which represents the stages of deep sleep and is thought to mark a restorative process.[36-38]

From our descriptive study, we cannot infer causal relationships, nor can we disentangle temporal associations. Our findings might nevertheless indicate that the experience of physical and psychological symptoms, including fatigue, and poorer sleep, perceived health, and functioning, may interact and reinforce one another, adding to the continuation of symptoms and impaired functioning.

Strengths and weaknesses

To our knowledge, this is the first time that a large primary care cohort of fatigued patients has been followed up with repeated measurements over a period of 12 months. Because of our large sample size and use of repeated measurements of multiple outcomes, we were able to distinguish between patients with different patterns of fatigue and associated variables over time. We aimed to describe trajectories of fatigue. Longitudinal analyses assessing individual associations over time are needed to give more insight into the temporal relationships between variables.

The completion rates of 82% to 88% during follow-up were high, and there was no selective dropout in terms of severity of fatigue. Participants and completers were somewhat older than nonparticipants and noncompleters, and this difference may have slightly influenced our findings, as older patients may more often report chronic fatigue. We did not find any differences in mean age between the 4 subgroups with a different course of fatigue, however. Participants were more often female than nonparticipants, and women more often had a chronic or recurrent course of fatigue compared with men

(60% vs 48%), while women were less likely to have a fast recovery (14% vs 28%). The generalizability of our results might not be optimal for younger and male patients; however, it is unlikely that the associations we found between different outcomes were influenced by this selective nonparticipation.

Implications for general practice and further research

Our findings indicate that among patients consulting their general practitioner because of fatigue, most of the improvement in both fatigue and functional impairment occurred 1 to 4 months after baseline; however, only 17% of patients showed a fast recovery. More than half of the patients (58%) had a course of recurrent or chronic fatigue with minimal changes over the year. To identify these patients, general practitioners should pay attention to patients' functioning, psychological symptoms, and sleep quality, especially in patients who are already chronically fatigued at presentation. Additionally, future research is needed to analyze the predictive value of these and other characteristics, which may provide handholds for more targeted treatment of fatigue in primary care.

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Stress takes you away from you all the time. *Yogi Bhajan*

5

Prediction of outcome in patients presenting with fatigue in primary care

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Abstract

Background
Although fatigue is a common problem presenting to primary care, few prospective studies have examined the contribution of a wide range of prognostic factors.

Aim
To determine the combination of factors most strongly associated with a favourable or unfavourable course of fatigue, when fatigue is presented as a main symptom in primary care.

Design of study
Prospective, observational cohort study with a 1-year follow-up.

Setting
A total of 147 primary care practices in the Netherlands.

Method
Patients presenting with fatigue as a main symptom completed questionnaires at baseline, and 1, 4, 8, and 12 months later. The prognostic value of potential predictors was assessed by applying multivariable logistic regression analysis. The outcome was severity of fatigue, defined as a combination of dichotomised scores on several repeated measurements with the Checklist Individual Strength. Separate models were used to predict either a favourable or an unfavourable course of fatigue.

Results
Baseline severity of fatigue and patient expectations of chronicity consistently predicted a poor outcome. Additional factors predicting a chronic course were baseline pain intensity and less social support. Baseline characteristics predicting a fast recovery were: male sex, not providing care for others (for example, for older people), better perceived health, and fewer (serious) prolonged difficulties. Both models had good reliability and discriminative validity (area under the receiver operating characteristic curve after internal validation: 0.78 and 0.79).

Conclusion
The identified combination of predictors reflects the multidimensionality of fatigue, with a significant contribution of patient expectations of chronicity in the prediction of a poor prognosis. These negative perceptions are modifiable, and should receive more attention in the initial assessment of patients presenting with fatigue.

Introduction

Fatigue is a common problem presenting to primary care.[1–4] In many cases, there is no apparent explanatory or accompanying disorder, and many patients do not return to visit the GP. However, the results of previous studies indicate that more than half of patients do not show a favourable course.[3,5,6] It is likely that the occurrence and persistence of this nonspecific symptom is determined by multiple factors. Nonetheless, a systematic review of the literature revealed that only a few prospective studies in primary care have investigated the contribution of different prognostic factors; these studies did not include factors like lifestyle and social factors. The possibility of building a prognostic model also depends on the sample size; most of the studies that have been performed had fairly small study populations. Furthermore, few studies enrolled patients who presented with fatigue as a main symptom.[7] To improve GPs' history taking and management of this frequently presented nonspecific symptom, it is important to know which factors are likely to be relevant in predicting the outcome of an episode of fatigue. The aim of this study was to include a sufficiently large sample to investigate which combination of factors predicts a favourable or unfavourable course of fatigue when presented as a main symptom in primary care. A wide range of potential prognostic factors was investigated, by addressing sociodemographic factors, fatigue characteristics, and somatic, psychological, social, and lifestyle factors.

Method

Design and recruitment

An observational cohort study of adult patients presenting with fatigue as a main symptom was conducted in 147 practices across the Netherlands. From June 2004 to January 2006, 111 GPs and 57 GP trainees recruited patients with a new episode of fatigue. This implied that the patient had neither visited the GP before for the same episode of fatigue, nor visited for a previous episode within the past 6 months. Patients who were receiving or had received chemotherapy or radiotherapy during the 3 months before the consultation, and women who were pregnant or less than 3 months postpartum, were excluded. Eligible patients were informed by their GP about the study and invited to participate. If interested, they were sent an information letter and the baseline questionnaire. Patients were enrolled if they then returned the signed consent form. Participants completed these questionnaires shortly after the consultation (baseline), and at 1, 4, 8, and 12 months after baseline.

Definition of outcome

Outcome was defined in terms of both recovery and chronicity, assessed with the severity scale of the Checklist Individual Strength (CIS).[8] The CIS is a 20-item questionnaire that has been validated in several study populations with fatigue in the Netherlands, and recently in Taiwan and Japan (7 point Likert scale from 'Yes, true' to 'No, not true'). A score of 34 or higher on the eight-item subscale for subjective fatigue has often been used as a cut-off point for severe fatigue.[9,10] Both the study's outcome definitions were based on multiple outcome measurements during follow-up. Recovery was defined as a score of <34 on the severity scale of the CIS at 4, 8, and 12 months after baseline. An unfavourable course (chronic fatigue) was defined as a score of ≥34 on the CIS severity scale, at three or all of the four follow-up measurements. Patients with missing measurements during follow-up were only classified as recovered or chronically fatigued if sufficient measurements were available.

Potential predictors

Data on baseline patient characteristics that were analysed as potential predictors were mainly obtained from the postal questionnaire and measured with validated questionnaires if available. Demographic variables included age, sex, education, paid work, hours of work, marital status, and providing care for others. Fatigue characteristics included duration, onset, location, previous episodes, and baseline levels of fatigue according to the subscales of the CIS (severity scale, reduced motivation, reduced concentration). Attributions related to fatigue (virus or germ, diet or eating habits, altered immunity) and number of symptoms experienced since the start of fatigue were measured with the Illness Perception Questionnaire - Revised (IPQ-R).[11] A subscale for psychological attributions was developed, based on six individual items from the IPQ-R (stress or worry, my own behaviour, my mental attitude, family problems or worry, my emotional state, my personality; total score range 6–30; Cronbach's alpha 0.80). Other perceptions related to fatigue, measured with the IPQ-R, included personal control, coherence of symptoms, expectations of chronicity, and negative consequences. Psychological symptoms (distress, depression, anxiety, somatisation) were measured with the Four-Dimensional Symptom Questionnaire (4DSQ)[12], and sleep problems were measured with a subscale of the SCL-90 Checklist.[13] Perceived health and pain were measured with the Short-Form health survey-36 (SF-36).[14] Lifestyle factors included physical activity, measured with the Short Questionnaire to Assess Health-enhancing activity (SQUASH)[15], alcohol consumption, and smoking. Social factors were measured with adapted checklists for long-term difficulties and life events[16] and the Social Support Scale (SOS).[17] Additional questions about enjoyment of daily activities and mental strain during daily activities were also included. Data on relevant chronic diseases, malignancies, and functional syndromes were obtained from general practice records.

Statistical analysis

Logistic regression analysis was applied to determine the combination of factors that best predicted the outcome of fatigue. Two separate models were built, using two different outcome measures: recovery and chronicity. All patients from the total cohort providing sufficient data to define outcome were included in the models. First, univariate analysis was performed to examine the relationship between each potential predictor and outcome. For continuous variables, linearity of the associations with outcome was checked. If there was no linear trend, the variable was divided into categories, if possible based on existing cut-off points, otherwise in tertiles. Variables with *P*-value <0.20 (Wald statistic) were considered to be potential candidates for the multivariate analysis. Next, correlations between candidate variables were assessed. If there were strong inter-correlations (r>0.50), variables with weaker associations with outcome, or variables measuring a very similar construct, were excluded from the multivariate analysis. As the number of variables exceeded one-tenth of the number of patients with the outcome of interest, variables were entered in blocks, mainly adhering to the sequence of history taking in primary care (demographic factors first, followed by fatigue characteristics, then perceptions, health, and other symptoms, and finally lifestyle and social factors). Variables with a *P*-value >0.10 (Wald statistic) were removed manually in a stepwise backwards procedure, until all variables showed a significant association with outcome (*P*<0.10).

Evaluation of the models

The reliability of the models was determined by calibrating the observed frequencies against the predicted outcome probabilities in a calibration plot.[18] In this plot, perfect agreement between predicted and observed values results in a 45° line with a slope equal to 1 and an intercept equal to 0. In addition, the Hosmer–Lemeshow goodness-of-fit statistic was used to test whether there was any significant difference between predicted and observed values. The discriminative ability of the models was assessed by calculating the area under the receiver operating characteristic curve. A value of 1 for the area under the curve (AUC) indicates optimal discrimination between people with and without the outcome of interest, whereas a value of 0.5 indicates no discrimination above chance.[19] The internal validity of the models was assessed with a bootstrapping procedure (200 samples) to correct the AUC for over-optimism, in order to obtain an estimation that better reflects model performance in another, but similar population of patients with fatigue.[19,20] These analyses were performed using R statistics software (version 2.5.0).

Results

Response

GPs enrolled 856 patients; 642 consented to participate and completed the first questionnaire (response rate 75%). Baseline characteristics are presented in Table 5.1. Mean age was 42 years, and 60% of the patients had been fatigued for at least 6 months. Reasons for non-response were given by 127 patients (60% of those who did not participate), and the most frequently mentioned reasons were recovery from fatigue (43%) or lack of time or interest (32%); 8% reported that they were too tired, 4% were not eligible, and 13% were unwilling to participate for other reasons. On average, participants were 5 years older $P<0.01$) and included more women (73% versus 65%, $P<0.05$) compared to non-participants. During follow-up, the completion rates varied between 82% and 88%. No difference was found in fatigue severity or sex ratio between completers and noncompleters, but the completers were, on average, 8 years younger ($P<0.001$). Sufficient data were from 561 patients available to define a favourable outcome (recovery), and from 535 patients to define an unfavourable outcome (chronicity).

Table 5.1 Baseline characteristics of patients presenting with fatigue in general practice

	Number of patients (%) or mean (SD)		
	Total population (n=642)	Fast recovery (n=132)	(Near) chronicity (n=231)
Demographic			
Gender (female)	467 (73%)	84 (64%)	178 (77%)
Age (mean, SD)	42 (16)	43 (15)	45 (17)
Education			
Primary	40 (6%)	6 (5%)	19 (8%)
Secondary	483 (75%)	102 (77%)	173 (75%)
College/university	118 (18%)	24 (18%)	38 (17%)
Care for children	241 (38%)	56 (43%)	83 (36%)
Care for children <5 years old	103 (16%)	23 (17%)	31 (14%)
Care for other people (e.g. elderly)	63 (10%)	4 (3%)	27 (12%)
Employed	492 (77%)	107 (81%)	160 (69%)
Hours of work (paid + unpaid) per week (mean, SD)	41 (26)	44 (19)	40 (29)
<30	182 (28%)	23 (17%)	77 (34%)
30-50	277 (43%)	66 (50%)	97 (42%)
≥50	183 (29%)	43 (33%)	56 (24%)
Living together/married	411 (64%)	85 (64%)	144 (63%)
Fatigue (mean, SD)			
Severity (CIS)	45.8 (8.4)	41.4 (9.5)	48.9 (6.5)
Less concentration (CIS)	21.3 (8.7)	16.1 (6.0)	22.5 (8.7)
Less motivation (CIS)	16.9 (6.2)	18.7 (8.3)	17.6 (6.3)

Table 5.1 (continued)

	Number of patients (%) or mean (SD)		
	Total population (n=642)	Fast recovery (n=132)	(Near) chronicity (n=231)
Duration of fatigue			
< 1 month	44 (7%)	15 (12%)	15 (7%)
1-3 months	98 (16%)	32 (25%)	20 (9%)
3-6 months	115 (19%)	28 (22%)	40 (18%)
6-12 months	114 (18%)	21 (16%)	39 (17%)
≥ 1 year	252 (40%)	34 (26%)	112 (50%)
Onset of fatigue episode			
Sudden	111 (17%)	28 (21%)	37 (16%)
Gradual	527 (82%)	104 (78%)	191 (84%)
Previous episodes			
Yes	417 (65%)	66 (50%)	163 (71%)
Yes, duration < 6 months	246 (38%)	46 (35%)	76 (33%)
Yes, duration ≥ 6 months	171 (27%)	20 (15%)	87 (38%)
Localisation of fatigue			
Primarily extremities	56 (9%)	19 (14%)	19 (8%)
Primarily head	111 (17%)	29 (22%)	29 (13%)
Whole body, or head and extremities	407 (64%)	70 (53%)	162 (70%)
Not clear	66 (10%)	14 (11%)	21 (9%)
Cognitions (IPQ-R; range) (mean, SD)			
Personal control (6-30)	18.6 (3.7)	19.2 (3.7)	17.9 (3.8)
Understanding of the fatigue (5-25)	13.7 (4.2)	14.1 (4.2)	13.2 (4.1)
Expectation of a chronic course (6-30)	17.4 (4.5)	15.2 (3.6)	19.4 (4.6)
Impact of fatigue (6-29)	16.4 (4.3)	14.4 (3.9)	18.0 (4.3)
Treatment (self-report)			
Treatment for fatigue	52 (8%)	8 (6%)	28 (12%)
Treatment for other reasons	181 (28%)	38 (29%)	76 (33%)
Medication	146 (23%)	32 (24%)	57 (25%)
Psychologist or social work	44 (7%)	8 (6%)	22 (10%)
Physio- or manual therapy	63 (10%)	9 (7%)	32 (14%)
Alternative/complementary treatment	40 (6%)	11 (8%)	13 (6%)
Daily activity and lifestyle			
Physical activity (SQUASH; number of days of moderate intensity physical activity for at least 30 minutes)			
mean (SD)	2.8 (2.4)	3.1 (2.2)	2.8 (2.5)
0	147 (23%)	22 (17%)	54 (23%)
1-4	319 (50%)	70 (53%)	113 (49%)
≥ 5	175 (27%)	39 (30%)	64 (28%)
Alcohol (units per week)			
< 1	334 (52%)	59 (45%)	131 (57%)
1-10	253 (40%)	64 (49%)	80 (35%)
> 10	54 (9%)	9 (7%)	20 (10%)
Smoking			
No, never smoked	253 (40%)	56 (42%)	89 (39%)
Not currently, or sometimes	242 (38%)	52 (39%)	85 (37%)
Yes, daily	145 (23%)	24 (18%)	56 (24%)

SD=standard deviation; CIS=Checklist Individual Strength; IPQ-R=Illness Perception Questionnaire-Revised; SQUASH=Short Questionnaire to Assess Health enhancing activity.

Favourable course: recovery within 4 months

A total of 132 patients (24%) showed a favourable course of fatigue. Outcome predictors are presented in Table 5.2. Of 41 potential variables, 26 showed a significant association ($P<0.20$) in the univariate analysis and were entered in blocks in a multivariate model. The following combination of factors was most strongly associated with a favourable course: not providing informal care for others, less severe fatigue at baseline, no expectations of chronicity, less (serious) prolonged difficulties, male sex, and better perceived health. The AUC increased from 0.60, based on the first block (demographic variables only), to 0.79 (95% CI 0.74 to 0.83) for the final model; most of the subsequent gain in discriminative ability was obtained after adding the second block, which included characteristics of fatigue (AUC 0.76). The corrected AUC after internal validation was 0.78. The reliability of the model was good; the calibration plot (Figure 5.1) shows that the observed and predicted probabilities of a positive outcome were fairly close to the 45° line. The Hosmer–Lemeshow statistic showed no significant difference between observed and predicted values ($P=0.22$).

Unfavourable course: (near) chronicity

A total of 231 patients (43%) showed an unfavourable course of fatigue. Twenty-nine variables showing a significant univariate association were entered in blocks in the multivariate model. The prognostic factors that were retained in the model were severity of fatigue, expectations of chronicity, more pain, and less social support (Table 5.2). The AUC increased from 0.57 to 0.80 (95% CI 0.76 to 0.84) in the final model; again, baseline characteristics of fatigue contributed most to the predictive performance (AUC 0.74). The corrected AUC after internal validation was 0.79. The reliability of this model was confirmed by visual inspection of the calibration plot (Figure 5.2) and by the Hosmer–Lemeshow statistic ($P=0.38$).

Table 5.2 Predictors of outcome in patients presenting with fatigue (short version, final models)

	Odds Ratio (95% CI)	
	Favourable course (n=561); AUC 0.79)	Unfavourable course (n=535 ; AUC 0.80)
Gender (female vs male)	0.64 (0.40 – 1.03)	
Care for others (e.g. elderly) (yes)	0.23 (0.07 – 0.71)	
Fatigue severity (CIS; p.p.i.)	0.93 (0.90 – 0.96)	1.08 (1.05 – 1.11)
Expectations of chronicity (IPQ-R; p.p.i.)	0.88 (0.83 – 0.93)	1.19 (1.13 – 1.25)
Better perceived health (SF-36; p.p.i.)	1.01 (1.00 – 1.03)	
Less pain (SF-36; p.p.i)		0.98 (0.97 – 0.99)
More (serious) prolonged difficulties (p.p.i.)	0.93 (0.88 – 0.99)	
Less social support (SOS; p.p.i.)		1.03 (1.01 – 1.06)

AUC= area under the curve; CIS=Checklist Individual Strength; p.p.i.= per point increase; IPQ-R=Illness Perception Questionnaire-Revised; SF-36= Short Form health survey-36; SOS=Social Support Scale.

Chronic disease

In the total cohort, 60 patients (11% of 525) had a chronic condition that could be considered to be present at the time of consultation, notably asthma or chronic obstructive pulmonary disease (*n*=37, 7%) or diabetes (*n*=17, 3%). Fourteen patients (3%) had a malignancy in their medical history, and 20 patients (4%) had a functional syndrome, most often irritable bowel syndrome (*n*=17, 3%). Within the group showing an unfavourable course, 26 patients (14% of 190 with available data on comorbidity) had a chronic condition, compared to 11 patients (10% of 112) in the group showing a favourable course. Because data on comorbidity were not available for 17% of the patients, chronic disease was not included in the prognostic analysis.

Figure 5.1 Calibration plot for prediction of a favourable course of fatigue

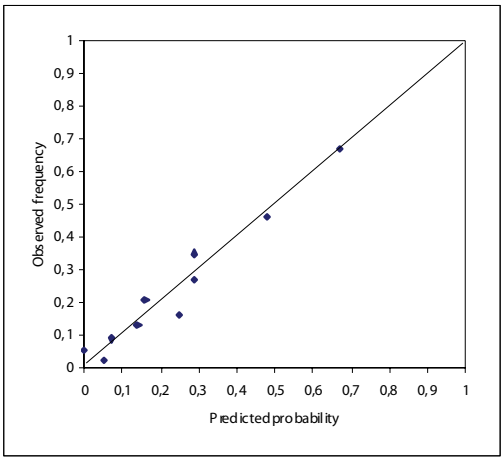

Figure 5.2 Calibration plot for prediction of an unfavourable course of fatigue

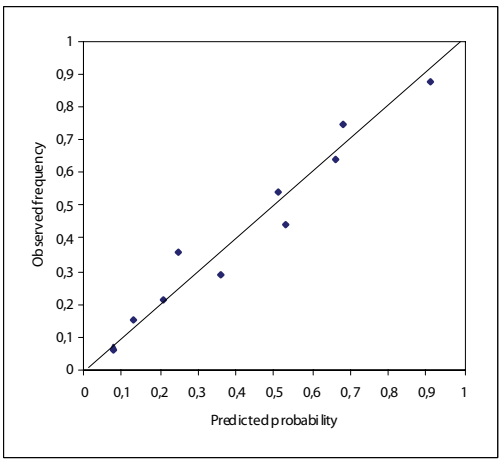

Table 5.2 Predictors of outcome in patients presenting with fatigue in general practice

	Favourable course (n=561)			Unfavourable course (n=535)		
	Univariate OR (95% CI)	P*	Multivariate OR (95% CI) (AUC 0.79)	Univariate OR (95% CI)	P*	Multivariate OR (95% CI) (AUC 0.80)
Demographic characteristics						
Gender (female vs male)	0.51 (0.33 - 0.77)	0.001*	0.64 (0.40- 1.03)	1.46 (0.98 - 2.16)	0.059*	
Age						
Per year older				1.01 (1.00 -1.02)	0.059*	
31-50 vs. 18-30	1.44 (0.87 - 2.39)	0.16				
51-89 vs. 18-30	1.40 (0.81 - 2.42)	0.24				
Education						
Secondary vs. primary	1.44 (0.58 - 3.57)	0.44		0.66 (0.33 - 1.32)	0.24	
College/university vs. primary	1.33 (0.49 - 3.61)	0.57		0.48 (0.22 - 1.04)	0.062	
Care for children < 5 years old (yes)	1.01 (0.60 - 1.69)	0.98		0.80 (0.49 - 1.30)	0.37	
Care for others (e.g. elderly) (yes)	0.24 (0.09 - 0.68)	0.004*	0.23 (0.07-0.71)	1.39 (0.79 - 2.43)	0.26	
Hours of work (per week)	1.01 (1.00 - 1.01)	0.23		1.00 (0.99 -1.00)	0.22	
Employed (yes)	1.70 (1.03 - 2.79)	0.048*		0.63 (0.42 - 0.93)	0.023*	
Married or living together (yes)	0.91 (0.61 - 1.38)	0.67		0.86 (0.60 - 1.23)	0.41	
Fatigue						
Fatigue severity (CIS, p.p.i.)	0.91 (0.89 - 0.93)	<0.001*	0.93 (0.90 – 0.96)	1.10 (1.07 – 1.13)	<0.001*	1.08 (1.05 – 1.11)
Less concentration (CIS,p.p.i.)	0.96 (0.94 – 0.98)	<0.001*		1.04 (1.02 – 1.06)	<0.001*	
Less motivation (CIS,p.p.i.)	0.97 (0.94 – 1.00)	0.066*		1.03 (1.00 – 1.06)	0.024	
Duration						
3-6 months vs. < 3 months	0.68 (0.39 – 1.19)	0.18*		1.80 (1.03 – 3.15)	0.039*	
6-12 months vs. < 3 months	0.47 (0.26 – 0.86)	0.013*		2.00 (1.13 – 3.52)	0.017*	
≥ 12 months vs. < 3 months	0.32 (0.19 – 0.54)	<0.001*		3.13 (1.95 – 5.04)	<0.001*	
Previous episodes (yes)	0.42 (0.28 – 0.63)	<0.001*		1.41 (0.98 – 2.03)	0.067*	
Onset (sudden vs. gradual)	0.66 (0.40 – 1.08)	0.096*		0.99 (0.62 – 1.58)	0.97	
Fatigue in whole body or several body parts vs. locally (only head or limbs)	0.53 (0.36 – 0.79)	0.001*		1.67 (1.16 – 2.40)	0.005*	
Perceptions (IPQ-R)						
Personal control (p.p.i.)	1.06 (1.01 – 1.12)	0.026*		0.91 (0.87 – 0.96)	<0.001*	
Coherence of fatigue symptoms (p.p.i.)	1.03 (0.98 – 1.08)	0.21		0.94 (0.90 – 0.98)	0.003*	
Expectations of chronicity (p.p.i.)	0.84 (0.80 – 0.89)	<0.001*	0.88 (0.83 – 0.93)	1.23 (1.17 – 1.29)	<0.001*	1.19 (1.13 – 1.25)
Negative consequences (p.p.i.)	0.85 (0.81 – 0.90)	<0.001*		1.18 (1.13 – 1.24)	<0.001*	
Psychological attribution (from IPQ-R, (p.p.i.)	0.94 (0.90 – 0.98)	0.007*		1.02 (0.99 – 1.06)	0.23	
Viral/germ attribution (yes)	1.32 (0.85 – 2.05)	0.22		0.84 (0.57 – 1.25)	0.40	
Altered immunity attribution (yes)	0.66 (0.43 – 1.01)	0.06*		1.31 (0.91 – 1.88)	0.15*	
Diet/eating habits attribution (yes)	0.72 (0.42 – 1.24)	0.23		1.61 (1.02 – 2.55)	0.040*	

	Favourable course (n=561)			Unfavourable course (n=535)		
	Univariate OR (95% CI)	P*	Multivariate OR (95% CI) (AUC 0.79)	Univariate OR (95% CI)	P*	Multivariate OR (95% CI) (AUC 0.80)
Health and other symptoms						
Better perceived health (SF-36, p.p.i.)	1.03 (1.02 – 1.05)	<0.001*	1.01 (1.00 – 1.03)	0.97 (0.96 – 0.98)	<0.001*	
Less pain (SF-36, p.p.i.)	1.02 (1.01 – 1.03)	<0.001*		0.97 (0.97 – 0.98)	<0.001*	0.98 (0.97 – 0.99)
Distress (4DSQ, p.p.i.)	0.93 (0.91 – 0.96)	<0.001*		1.06 (1.04 – 1.09)	<0.001*	
Depression (4DSQ, p.p.i.)	0.86 (0.78 – 0.95)	0.002*		1.21 (1.12 – 1.30)	<0.001*	
Anxiety (4DSQ, p.p.i)	0.87 (0.81 – 0.94)	<0.001*		1.10 (1.05 – 1.16)	<0.001*	
Somatisation (4DSQ, p.p.i.)	0.91 (0.88 – 0.95)	<0.001*		1.10 (1.07 – 1.13)	<0.001*	
Sleep problems (SCL-90)						
Above average vs. low or average	1.10 (0.64 – 1.89)	0.73		0.81 (0.49 – 1.33)	0.40	
High vs. low or average	0.82 (0.51 – 1.30)	0.39		1.22 (0.81 – 1.83)	0.34	
Number of experienced symptoms since start of fatigue (IPQ-R)	0.85 (0.78 – 0.92)	<0.001*		1.14 (1.07 – 1.22)	<0.001*	
Social factors and lifestyle						
Number of days of moderate intensity physical activity for at least 30 min. (SQUASH)						
Continuous	1.07 (0.99 – 1.16)	0.11*				
1-5 days vs. 0 days				0.81 (0.53 – 1.26)	0.35	
5-7 days vs. 0 days				0.96 (0.59 – 1.57)	0.86	
Physical activity of vigorous intensity in work, school or household (SQUASH)						
< 5 hours vs. no	1.08 (0.68 – 1.71)	0.74		0.82 (0.54 – 1.25)	0.36	
≥ 5 hours vs. no	0.72 (0.44 – 1.17)	0.18		0.99 (0.66 – 1.49)	0.97	
Enjoying daily activities (yes)	1.88 (1.20 – 2.94)	0.005*		0.60 (0.42 – 0.87)	0.006*	
Mentally strenuous daily activities (yes)	0.83 (0.56 – 1.24)	0.37		1.13 (0.80 – 1.60)	0.50	
More (serious) prolonged difficulties (checklist.; p.p.i)	0.89 (0.84 - 0.95)	<0.001*	0.93 (0.88 – 0.99)	1.09 (1.05 – 1.14)	<0.001*	
Life events (checklist)						
1 vs. 0	1.03 (0.62 – 1.73)	1.03		0.97 (0.62 – 1.53)	0.90	
≥ 2 vs. 0	0.81 (0.51 – 1.31)	0.81		1.20 (0.80 – 1.82)	0.38	
Less social support (SOS, p.p.i.)	0.96 (0.93 – 0.98)	0.002*		1.05 (1.03 - 1.07)	<0.001*	1.03 (1.01 – 1.06)
Alcohol (number of glasses in 5 categories; per category)	1.11 (0.97 – 1.28)	0.14*		0.90 (0.79 – 1.03)	0.11*	
Smoking (daily vs. sometimes, ever or never)	0.76 (0.46 – 1.25)	0.27		1.48 (0.97 – 2.26)	0.065*	

*Univariate p-values <0.20 were selected for multivariate analysis. OR=Odds Ratio; CI=confidence interval; AUC=area under the curve; CIS=Checklist Individual Strength; p.p.i.=per point increase; IPQ-R=Illness Perception Questionnaire-Revised; 4DSQ=Four-Dimensional Symptom Questionnaire; SCL=Symptom Checklist; SF-36=Short Form health survey 36; SOS=Social Support Scale.

Discussion

Summary of main findings
During the year following the consultation, a minority of the patients reported recovery within 4 months, while a substantial number of patients showed an unfavourable course. The combination of factors that best predicted the course of fatigue reflected different dimensions: demographics, fatigue characteristics, perceptions, general health, psychological, and social factors. This corresponds well with the concept that fatigue is a multidimensional problem. Consistent and significant predictors of an unfavourable outcome in both models were baseline severity of fatigue and patient expectations of chronicity.

Strengths and limitations of the study
Instead of measuring the outcome at one moment in time, the outcomes of repeated measurements during one year were combined to define a favourable or unfavourable course. This may have resulted in a more stable outcome, and thus have strengthened the results. Separate analyses were performed for patients with either a good or a poor outcome, because this provided information about relevant subgroups of patients, and may help GPs in their decision making with regard to management of the problem.

By assessing the relative contribution of a variety of potentially relevant prognostic factors, addressing somatic, psychological, and social problems, the multidimensional nature of the symptom was taken into account. Although some potential predictors may have been missed (for example, occupational health or spiritual beliefs), the study included a variety of factors that can be measured by means of questionnaires in a large-scale observational cohort study.

Clinical management could also account for variation in outcome. Although self-report data on treatment were collected, it was decided not to use this information in the prognostic models. In this observational study, confounding by indication would result in misleading information about the predictive value of management decisions.
Although the drop-out rate was low it was not possible to define the course of fatigue in each patient. It is unlikely, however, that this has strongly affected the composition of our prognostic models. Furthermore, notwithstanding the performance of the models, the results need to be validated in other populations of patients presenting with fatigue.

Apart from perceived health, no factors were found that were positively associated with a fast recovery. However, the contribution of negative perceptions to prognosis would imply that positive (or neutral) perceptions would have a positive effect on the course of fatigue. Investigating (coping) behaviour, patterns of activity, and diet in future studies

could reveal additional prognostic factors that are potentially modifiable and may provide alternative starting points for the development of interventions.

Comparison with existing literature

Baseline severity of fatigue has been found to be a prognostic factor in other studies in primary care[21], and in the community.[9,22,23] Duration of fatigue was found to be a prognostic indicator of outcome in other studies[6,24], but was not retained in the present study model; neither was localisation of fatigue. Both characteristics are apparently strongly related to severity, but their contribution was not significant in combination with fatigue severity. Rather than fatigue duration at baseline, patient expectations of chronicity significantly predicted an unfavourable course of fatigue in both models. Similar results have been found for poor fatigue outcome after 6 months in a previous study in primary care.[25] Furthermore, more personal control or self-efficacy has been shown to be associated with a better prognosis in fatigued employees on sick leave[26], and patients with chronic fatigue syndrome[27], which may indicate that more personal control can result in more positive expectations regarding the course of the fatigue and, subsequently, in better outcomes.

The prognostic value of patient expectations might explain why psychological symptoms were not retained in the models. Previous studies that reported associations of psychological symptoms with fatigue outcome did not measure illness-related perceptions.[21,28] Likewise, contrary to findings from other studies[9,25–27], patient attributions were not retained in this study's models. This might be partly explained by the fact that patients often have mixed attributions; an exclusively somatic illness attribution may have more predictive value than the presence of a psychological attribution. More importantly, patient attributions may be related to expectations of chronicity. These catastrophising perceptions were consistently retained in both models, and were apparently more important in predicting outcome in this study's population. Apart from psychological symptoms, the number of other physical symptoms and pain intensity were also related to a poor outcome, whereas better perceived health was related to a favourable outcome. These results are in line with the results of studies among employees with fatigue.[26,29]

Female sex, providing informal care, and more (severe) prolonged difficulties were included in the combination of factors that were inversely associated with a fast recovery. This seems to indicate a negative influence of higher levels of external demands. Caring for young children has been reported to be associated with fatigue in a cross-sectional nationwide study[30] and can be a sexspecific indication of more responsibilities, but such an association was not found longitudinally. However, although less frequent in the present study population, providing informal care for other

adults (ill or older people) was a significant predictor. It could be hypothesised that taking care of children is generally a choice or a planned responsibility that takes place in another phase of life, and therefore might be perceived as less distressful or tiring.

A majority of 82% of the participants in this study reported that they experienced prolonged difficulties, and 17% experienced severe difficulties in at least one area. The associations of prolonged difficulties and social support with outcome are in line with studies among patients with chronic fatigue syndrome, showing that negative interactions or insufficient support contribute to the persistence of symptoms[31], and that negative or serious difficulties were more frequent in the months preceding the onset of chronic fatigue syndrome.[32,33] Furthermore, enjoying daily activities was univariately associated with a positive outcome in the current study, while the number of life events was not associated with a negative outcome. These findings would support the notion that perceived quality or intensity of activities or events may be more important than their number in contributing to the (im)balance between perceived demands and resources in patients with fatigue.

Implications for future research and clinical practice

Patient perceptions are associated with the prognosis of fatigue in primary care. Negative thoughts regarding symptoms are potentially modifiable in patients, and evaluation of the effectiveness of targeted interventions should be addressed in future research among patients presenting with fatigue in general practice. In the meantime, when taking a patient's history, GPs should pay attention to the presence of negative perceptions in patients who present with fatigue to identify those who are already at risk of a poor outcome at the time of the initial assessment.

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If there is awareness in you, you no longer need to believe in every thought you think. *Eckhart Tolle*

6

Fatigue in primary care: longitudinal associations with pain

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Abstract

So far, most studies on the association between pain and fatigue have used cross-sectional data. We analysed possibilities for a temporal relationship between pain and fatigue in a cohort study of patients presenting with fatigue in primary care. Of 856 recruited patients, 642 (75%) completed postal questionnaires after the consultation, and at one, four, eight and 12 months follow-up, with completion rates ranging from 82 to 88%. Pain was measured using the Short-Form health survey (SF-36) and fatigue using the severity scale of the Checklist Individual Strength (CIS). Longitudinal associations were analysed using generalized estimated equations (GEE). We used three different models assessing possible relationships between the symptoms in time, either in the same intervals or with a time-lag, suggesting either a synchronous or temporal association. The regression coefficients were strongest in the model assessing synchronous change, indicating that a one-point improvement in pain was associated with a 0.25 improvement in fatigue in the same time interval (adjusted for potential confounding). Baseline duration of fatigue and expectations of its future course significantly modified the association in this model, with stronger associations between changes in pain and fatigue found in patients with a shorter duration of fatigue or more positive expectations. The models using a time lag showed a significant but inverse association between changes in pain and subsequent changes in fatigue. The results indicate that changes in pain and fatigue are directly related in time, rather than showing temporal associations.

Introduction

Fatigue is a frequently presented nonspecific symptom in primary care, that has a long list of differential diagnoses, yet often remains unexplained.[28] Fatigue frequently co-occurs with other symptoms such as (musculoskeletal) pain, and the experience of multiple symptoms may increasingly add to limitations in functioning.[37] Although the association between pain and fatigue has been reported in both community studies and secondary care populations with chronic fatigue syndrome (CFS), fibromyalgia, rheumatoid arthritis or cancer, no studies on the temporal relationship between pain and fatigue have been performed in primary care populations.

Most studies that have been performed on the overlap between pain and fatigue have used cross-sectional data.[3,15,22,33,40] However, in a prospective cohort study among employees, a higher pain score predicted worse fatigue outcome after one year.[13] In a previously published predictive model, in which the association between variables measured at baseline only (including pain) and fatigue outcome at follow-up was presented, we found a similar association with higher pain scores predicting a higher probability of a chronic course of fatigue.[25] Furthermore, in subgroups of patients showing different trajectories of fatigue severity (chronic fatigue, recurrent fatigue, fast or slow recovery), levels of pain showed similar patterns in time.[26]

Longitudinal analysis is needed in order to assess whether fatigue and pain are consistently associated in time within patients: are changes in pain over time associated with (subsequent) changes in fatigue? Similar risk factors for fatigue and pain, and the finding of similar patterns in time suggest a proportionate relationship; this would yield a synchronous association between changes in fatigue and pain. Alternatively, fatigue may be a consequence of experiencing episodes of pain. However, a third possibility is that pain may be more easily experienced when feeling fatigued possibly because of a lowered pain threshold, which may be associated with processess of neuroimmunological dysregulation.[21] The finding that many pain-related diagnoses were made in our cohort of patients presenting with fatigue, mainly in the year after the consultation for fatigue, might indicate towards this third possibility.

Several factors, including sleep problems, level of distress, patients' expectations regarding the course of fatigue, and duration of fatigue at presentation might confound or modify the associations between fatigue and pain. Pain has been suggested to exacerbate sleep difficulties[24], and sleep problems have been suggested to be (part of) the cause of fatigue in pain patients[8], while conversely, sleep problems have been found to predict the onset of chronic widespread pain.[12] Increased levels of distress and negative expectations have been associated with an unfavourable outcome of both pain and fatigue,[6,19,26,27,35] and could therefore account for or modify the association between these symptoms. Finally, baseline duration of fatigue could confound or modify the

association between fatigue and pain, as patients experiencing chronic fatigue at baseline may also have chronic pain.

Considering these questions and hypotheses, our aim was to investigate the longitudinal association between fatigue and pain in patients presenting with fatigue in primary care, taking into account different possibilities for a temporal relationship: 1. changes in fatigue and pain show a synchronous association; 2. changes in pain are associated with subsequent changes in fatigue; 3. changes in fatigue are associated with subsequent changes in pain. We also explored the influence of sleep, distress, negative expectations and baseline duration of fatigue on the longitudinal association between pain and fatigue.

Methods

Participants

We conducted an observational cohort study among adult patients presenting with a main symptom of fatigue in 147 practices across the Netherlands. From June 2004 to January 2006, 111 GPs and 57 trainees recruited patients with a new episode of fatigue. This implied that the patient had neither visited the GP for the same episode of fatigue, nor for a different episode within the past six months. Patients who were receiving or had received chemotherapy or radiotherapy within three months before the consultation, and women who were pregnant or less than three months postpartum were excluded. Eligible patients were informed about the study by the GP, and invited to participate. If interested, they were sent an information letter and the baseline questionnaire. Patients were enrolled when they returned a signed consent form. Participants completed postal questionnaires shortly after the consultation (baseline), and at one, four, eight and 12 months after baseline.

Outcomes

Both fatigue and pain were measured at baseline and at each moment of follow-up. Pain was measured with the Short-Form health survey (SF-36), a widely used questionnaire for perceived health and functioning.[1,38] The pain scale consists of two items, both relating to the past four weeks. One item measures severity of pain on a 6-point Likert scale ('no pain' to 'very severe pain'). The other item measures the extent to which pain caused impairment in usual daily activities on a 5-point Likert scale ('not at all' to 'very much'). Standardised final scores range from 0-100, with higher scores indicating less pain. Fatigue was measured with the Checklist Individual Strength (CIS), which has been validated in several fatigued populations.[4,39] The CIS is a 20-item questionnaire, scored on a 7-point Likert scale. The severity scale consists of 8 items, with a score range

between 8-56. Questions relate to fatigue in the past two weeks. In order to facilitate interpretation and comparison of the regression coefficients, the fatigue subscale was also standardised to a scale ranging from 0-100 to yield similar final scales for pain and fatigue. Higher scores indicate more fatigue.

Potential confounders or effect modifiers

Apart from gender and age, we took account of four factors that could explain or modify the association between fatigue and pain. Levels of distress, sleep problems, duration of fatigue at baseline and expectations of a chronic course of fatigue were considered as potential confounders or effect modifiers of the association between changes in fatigue and pain, more or less directly influencing the association between both symptoms in either direction. Although sleep problems, distress and perceptions regarding symptoms may vary over time, only baseline values were available for these variables. Therefore all covariates in our models were time-independent.

Sleep problems were measured with a subscale from the SCL-90 Checklist, containing three items scored on a 5-point Likert scale (range 3-15).[2] Distress was measured with the Four-Dimensional Symptom Questionnaire (4DSQ), which has been validated in primary care populations.[34] The 4DSQ measures psychological distress, depression, anxiety and symptoms possibly indicating somatisation. The distress scale contains 16 items, resulting in a standardised score range between 0-32. Some examples of items are 'Did you become emotional easily in the past week?' and 'Did you feel that you could no longer cope with things in the past week?' Duration of fatigue at baseline was measured in number of months, and dichotomised at six months for analysis. Expectations regarding the course of fatigue were measured with the Illness Perception Questionnaire-Revised (IPQ-R); this scale comprises six items scored on a 5-point Likert scale, with a score range between 5-30.[23]

Statistical analysis

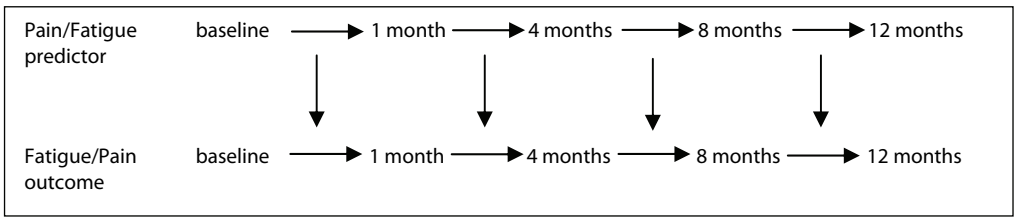
Descriptive statistics were used to present baseline characteristics and mean scores for pain and fatigue over the 12 months follow up period. Mean scores were calculated for the whole population and for 4 subgroups that were pre-defined according to different patterns of fatigue in terms of severity. These groups had either high (>34) or low (≤34) scores on the CIS at all time points during follow-up (chronic course, fast recovery); low scores from 4 months onwards (slow recovery) or a recurrence of high scores after initial improvement.[25]

We used Generalised Estimating Equations (GEE) with robust standard errors (SPSS 15.0) to model pain and fatigue over time. In order to gain a more complete picture of the longitudinal association between fatigue and pain, we used three models to assess this association (see Figure 6.1). In the first model, we investigated whether a change in fatigue over time was associated with a change in pain during the same time period

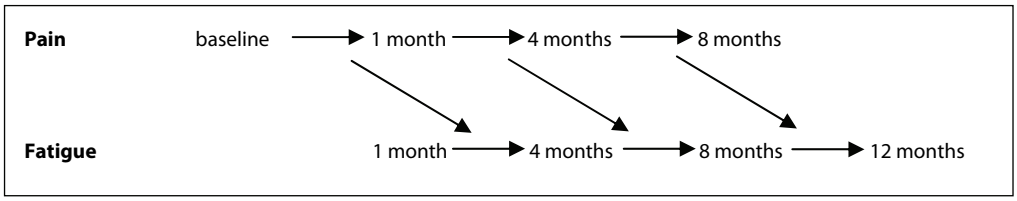
(model of change). As the analysis requires a distinction between predictor and outcome variables, this first model had two versions, either using change in fatigue, or change in pain as outcome variable. The second model addressed the question whether changes in fatigue would likely be a consequence of previous changes in pain. In this model, we studied the association between changes in pain in the first three measurement intervals during follow up, with changes in fatigue in the subsequent intervals. The third model was a reverse of the second model, assessing the associations of changes in fatigue with subsequent changes in pain.

Figure 6.1 Schematic representation of the models used to analyse the longitudinal association between fatigue and pain

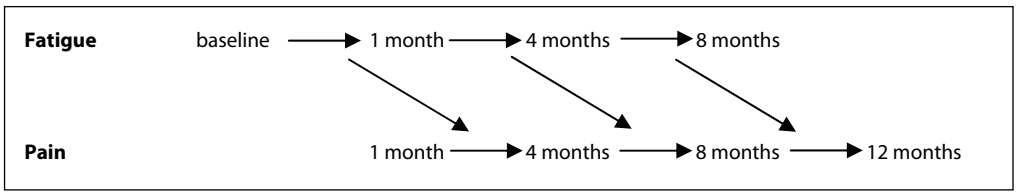
Model 1 – Model of change



Model 2 – Timelag model, outcome change in fatigue



Model 3 – Timelag model, outcome change in pain



GEE enables correction for dependency of observations within individuals over time, by choosing a 'working' correlation structure. In the analyses of all models we used an independent working correlation structure, which implies that within-person correlations between all measurements are equal to zero. This seemed to be the best option given the fact that adjustments were made for within-subject correlations by modelling of changes over time rather than absolute values at different time points.[36] GEE is assumed to be robust against the choice of an incorrect correlation structure.[39] To explore the confounding effects of age, gender, baseline levels of pain and fatigue, sleep problems, distress, baseline duration of fatigue and perception of the course, we added these factors (individually) to each model and studied changes in the estimated regression coefficients (crude versus adjusted) for the association between pain and fatigue. Next, to explore to what extent sleep problems, baseline levels of distress, duration of fatigue and negative expectations regarding the course of fatigue modified the association between changes in pain and in fatigue, we added interaction terms to the model, and checked direction and significance ($p<0.10$) of the interaction term.

Results

Population characteristics

Of 856 patients who were invited to participate, 642 (75%) gave informed consent and completed the baseline questionnaire. Participants in the study were on average five years older ($p<0.01$) and more often female (73% vs. 65%; $p<0.05$). Baseline characteristics are presented in Table 6.1. Completion rates during follow-up ranged from 82 to 88%. Completers were on average eight years older ($p<0.001$) compared to participants who were lost to follow-up. A majority of patients (58%) reported chronic fatigue (at least six months) at baseline.

Table 6.1 Patient characteristics at baseline

Patient characteristics	Number of patients (%) or mean (SD)
Age	41.8 (16.3)
Gender (female)	467 (73)
Married or living together	411 (64)
Care for children	242 (38)
Paid work	492 (77)
Educational level	
Primary	40 (6)
Secondary	483 (75)
College/university	118 (18)
Duration of fatigue	
<3 months	142 (23)
3-6 months	115 (19)
6-12 months	114 (18)
≥ 1 year	252 (40)
Distress (4DSQ; range 0-32)	
Baseline; 1 year	13 (7.4); 8.7 (7.0)
Sleep (SCL90; range 3-15)	
Baseline; 1 year	7.0 (3.1); 6.4 (2.7)
Expecting a chronic course of fatigue (IPQ-R; range 5-30)	17 (4.5)

4DSQ=Four-dimensional symptom questionnaire; SCL90=Symptom Checklist90; IPQ-R=Illness Perception Questionnaire-Revised.

The course of fatigue and pain over time in the total population gradually improved during the one-year follow-up (Table 6.2). The percentage of participants showing severe fatigue (original score >34) dropped from 90% at baseline to 45% after one year (data not shown). Figure 6.2 and 6.3 show mean changes in pain and fatigue over time in the predefined subgroups with different trajectories of fatigue. The results show similar patterns over time for both symptoms, although mean changes in fatigue are larger than changes in pain.

Table 6.2 Scores of pain and fatigue over time

	baseline	1 month	4 months	8 months	12 months
Fatigue	79 (17)	63 (23)	57 (26)	53 (28)	50 (28)
CIS serverity scale, standardised scores; mean (SD)	n=641	n=560	n=560	n=521	n=565
Pain	72 (24)	77 (24)	78 (24)	78 (25)	79 (24)
SF36; mean (SD)	n=642	n=561	n=560	n=522	n=566

CIS=Checklist Individual Strength; SF36=Short-Form Health Survey 36. Note: Higher scores on the fatigue scale indicate *more* fatigue, while higher scores on the pain scale indicate *less* pain

Figure 6.2 Standardised fatigue score in subgroups defined by fatigue severity over time
(higher scores indicate more fatigue)

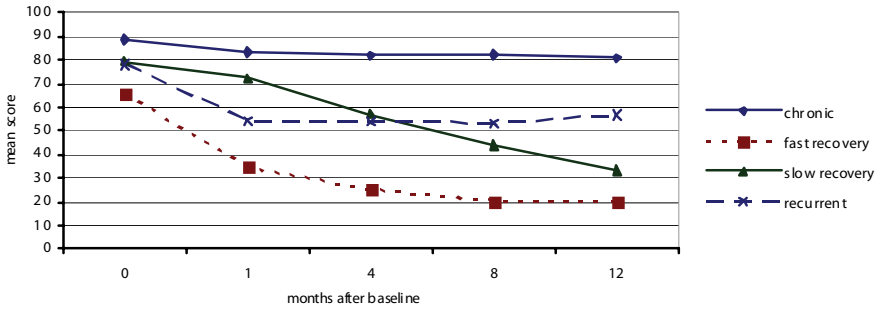
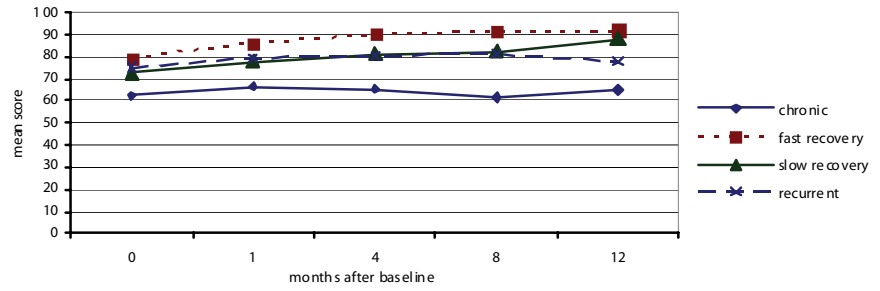


Figure 6.3 Pain score in subgroups defined by fatigue severity over time
(higher scores indicate less pain)



Model of change

The results of the GEE analysis, showing associations between fatigue and pain on an individual level, are presented in Table 6.3. The results of the first model, representing the association between changes in fatigue and pain over the same time intervals, showed a significant relation between changes in both symptoms ($p<0.001$), in both directions, with similar strength. Since the improvement of symptoms has an inverse direction on the scales of the CIS and SF36, the negative regression coefficients indicate that improvements in pain are associated with improvements in fatigue, and vice versa. The regression coefficients thus indicate that one point improvement in pain score corresponds with a 0.25 reduction, i.e. improvement in fatigue score, and a one-point increase in fatigue score corresponds with a 0.20 decrease, i.e. deterioration in pain score. In both models of change, the association was not confounded by baseline levels of pain or fatigue, age, gender, or any of the other four potential confounders. In the model using change in fatigue as outcome, a significant interaction was observed with negative expectations of the course of fatigue ($p=0.04$) and baseline duration of fatigue ($p=0.02$), but not for sleep problems ($p=0.83$) or level of distress ($p=0.99$). These

interactions indicate that for patients with chronic fatigue and patients with more negative perceptions, the association between changes in fatigue and pain is weaker than for patients with fatigue of shorter duration or with better expectations. In the inverse model of change, using change in pain as outcome, no interactions were observed.

Table 6.3 Longitudinal associations between fatigue and pain

	Crude model		Adjusted for baseline pain and fatigue		Adjusted model*	
	B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
Model of change, outcome: change in fatigue						
Predictor: change in pain	-0.27 (-0.31;-0.18)	<0.001	-0.26 (-0.33; 0.19)	<0.001	-0.25 (-0.31;-0.18)	<0.001
Model of change, outcome: change in pain						
Predictor: change in fatigue	-0.20 (-0.25; -0.15)	<0.001	-0.21 (-0.26; 0.16)	<0.001	-0.20 (-0.25; -0.15)	<0.001
Time lag model, outcome: change in fatigue						
Predictor: change in pain	0.12 (0.04; 0.19)	0.002	0.12 (0.04; 0.16)	0.002	0.12 (0.05; 0.20)	0.002
Time lag model, outcome: change in pain						
Predictor: change in fatigue	0.05 (-0.01; 0.11)	0.091	0.05 (-0.01; 0.11)	0.091	0.06 (-0.02; 0.12)	0.083

* Model adjusted for age, gender, baseline levels of pain, fatigue, sleep, distress and expectations of a chronic course of fatigue.
Note: Higher scores on the fatigue scale indicate *more* fatigue, while higher scores on the pain scale indicate *less* pain.

Models with time-lag

The second model, assessing the longitudinal relation between changes in pain and subsequent changes in fatigue, also showed a significant relationship ($p<0.01$). The positive regression coefficient indicates that an increase (i.e. improvement) in pain score was associated with a subsequent increase (i.e. deterioration) in fatigue score. Assessment of potential confounders and effect modification did not significantly change this association. The outcome of the third model, assessing the relation between changes in fatigue and subsequent changes in pain, did not show a significant association (Table 6.3).

Discussion

Main results

In this study we used three different models to analyse the longitudinal relationship between pain and fatigue in fatigued patients. The results suggest that the association is strongest in the model reflecting synchronous change in both symptoms. Adding a time-lag to the models resulted in an inversion of the regression coefficient in the model in which changes in pain predict subsequent changes in fatigue.

Contrary to our hypotheses, this result suggests an inverse relationship between changes in symptoms with a decrease in pain followed by an increase in fatigue (or vice versa). Several explanations may account for this finding. Part of the study participants showed a course of recurrent fatigue[25], resulting in increases in symptoms followed by decreases, and vice versa. Given the strong association between fatigue and pain within time intervals, this would result in decreases in pain being followed by subsequent increases in both pain and fatigue, and vice versa. This is supported by the fact that we found negative correlations between subsequent changes of either symptom, in all four subgroups with a different course of fatigue over time, indicating that an increase in pain (or fatigue) was followed by a decrease in pain (or fatigue) and vice versa. This results in an inverse relationship between both symptoms when a time lag is included in the model. Additional analyses for models 2 and 3 using average scores of the changes in pain and fatigue confirmed our findings by showing that average pain scores within intervals were positively associated with average fatigue scores in the next interval.

Thus, the results of the second and third model do not seem to support the hypotheses suggesting that changes in fatigue could be a consequence of changes in pain or vice versa. Rather, they do seem to strengthen our first hypothesis, indicating that symptoms of fatigue and pain are more closely related in time.

Effect modification

In a previous analysis[26], we showed that the extent to which patients expected their fatigue to last for a long time consistently predicted poor fatigue outcome in two prognostic models focusing on either chronic fatigue or fast recovery. In one of the models, pain also contributed to a chronic outcome of fatigue. Other studies have also shown the predictive value of expectations[6], coexisting pain[13] and also fatigue duration.[32] Several studies among pain patients have shown that negative expectations regarding pain recovery contributed to a poor outcome in terms of pain or return to work.[9,14,17] Therefore, these symptom perceptions are likely to worsen outcome of both (associated) symptoms; thus we expected that negative expectations or chronic fatigue would strengthen the association between the two symptoms.

These factors did not confound the association between pain and fatigue, and more importantly, in patients with chronic fatigue at baseline or negative expectations the

association between changes in fatigue and pain was weaker compared to patients with fatigue of short duration or more positive expectations. A possible explanation of this unexpected finding is that patients with negative perceptions and/or chronic fatigue are likely to be those who have more symptoms, including co-occurring pain, and may also show little change over time given the persistence and higher complexity of their symptoms. Furthermore, health perceptions and additional problems, for example anxiety or depressive symptoms may more strongly influence the course or impact of fatigue in these patients than co-existing pain. In any case, these findings merit further investigation.

Illness perceptions have been measured in a wide range of specific diseases or symptoms, frequently using an illness-specific version of the adaptable IPQ-R. We only measured perceptions regarding fatigue and did not include expectations of pain outcome. However, patient perceptions have also been shown to be more generally associated with health or (coping with) symptoms including both pain and fatigue[5,7,10], and considering the association between symptoms, it could be worthwhile to use more general rather than symptom-specific perceptions in future studies. Prior to this analysis, we assumed that expectations regarding fatigue could have a similar effect on pain as well, but these expectations did not modify the association in the model using change in pain as outcome. Although this may indicate a symptom-specific rather than a general effect, this result could also be related to the fact that fatigue was more of a problem in our population than pain, resulting in smaller changes in pain compared to fatigue outcome.
We selected a limited number of factors that might influence the association between pain and fatigue. However, other factors might be important in the co-occurrence of both symptoms. Self-efficacy did not predict outcome in our prognostic analysis[26], but is related to expectations of the course of symptoms, and has been associated with reporting both pain and fatigue[7,18,31], and multiple symptoms in general.[37] Chronic disease may also explain or modify the relationship between fatigue and pain. However, data on comorbidity and new diagnoses in this cohort show that very few patients had or received a diagnosis that is clearly indicative of severe pain, such as rheumatoid arthritis or cancer. Moreover, patients can experience fatigue and pain in a wide range of severity regardless of diagnosis, and in most cases these symptoms remain medically unexplained.

Strengths and limitations
To our knowledge no previous studies have analysed the longitudinal relationship between pain and fatigue in patients consulting the GP for fatigue. We studied these symptoms in a large cohort with five repeated measurements within one year. The advantage of longitudinal analysis is that the individual development of both fatigue

and pain in time can be investigated. Our results add epidemiological evidence to a direct association between pain and fatigue over time in individual patients.

A limitation of this study concernes the analysis of potentially confounding and modifying factors. Follow-up data on these factors were not available, while some of these factors, namely sleep problems, distress and perceptions are in fact also time dependent. Taking account of those factors seems to be important considering suggested (psycho)physiological mechanisms. Processes of both neuroimmunological dysregulation, resulting in central sensitisation, and neuroendocrine disturbance have been suggested to play a role in the occurrence of pain and fatigue symptoms in patients with CFS, chronic widespread pain and fibromyalgia.[20,21,29,30] Dysfunction of neuroendocrine processes has also been associated with disturbed sleep and distress.[20,29,30] Therefore, a repeated measurement of sleep and distress may reveal a confounding or modifying effect of these factors in the co-occurrence of fatigue and pain. To gain a better insight in the nature of the association between these symptoms, further longitudinal studies should take into account the time-dependent nature of potential modifying factors.

To answer our study question on the association between symptom change in both fatigue and pain, using equal time periods for the analysis would have been preferable. However, the main objective of our cohort study was to study the course of fatigue over time, and the timing of measurements in this cohort study was specifically chosen to optimally measure changes in fatigue following consultation. Although there is little knowledge on time patterns in biological processes relevant to fatigue, we expected most change in the first months, and therefore an additional assessment at one month was added. The difference between one or several months, however, may not be so critical when looking at temporal changes in multiple symptoms. Our hypothesis considered the *order* of changes in fatigue and pain in general, and the longitudinal analysis takes this into account, for the three different periods of time.

In contrast to fatigue, we did not have information on the duration of pain at baseline. Similar to the influence of fatigue duration on the relationship between fatigue and pain, the duration of pain could affect the occurrence of changes in fatigue as well. Furthermore, we used different scales for measuring fatigue and pain; since our study focused on patients with fatigue, our measurement of pain was less elaborate. The pain scale we used is well validated and has frequently been used, however, it consists of only two questions, with a limited number of response options, consequently leaving little room for detecting small changes. To gain more insight into longitudinal associations between both symptoms, it could be useful to use similar scales rating the severity (and impact) of symptoms. Our research question may also yield further insight when studied

in a population of patients with both fatigue and pain as a main symptom. Nevertheless, we were able to show a longitudinal association between changes in pain and fatigue in patients presenting with fatigue, confirming the importance of co-occurring symptoms in patients with fatigue.

Study implications

Experiencing multiple symptoms has been associated with poor functioning and psychological symptoms.[16,37] Increasingly severe and limiting pain or fatigue has been shown to be increasingly associated with co-occurring fatigue or pain, and people reporting both symptoms more often experience anxiety or depression.[7,11] Our study shows that changes in pain and fatigue are directly associated in time. Future research, including qualitative studies, should further address which factors contribute to the longitudinal association of these common symptoms.

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Ik heb geprobeerd alles zo goed mogelijk in te vullen, maar soms weet ik het gewoon niet wat de oorzaak is. *Deelnemer MOE*

7

General discussion

We studied the course, prognosis and diagnoses in a large cohort of patients presenting with fatigue as a main complaint in primary care. In this final chapter, the results of the foregoing chapters will be discussed in relation to each other and the literature. Subsequently, some methodological issues will be considered, and suggestions for further research and general practice will be made.

Fatigue in primary care: diagnoses and related symptoms

Within one year after presenting with fatigue, a minority of patients (8%) was diagnosed with organic pathology, a larger minority (16%) was diagnosed with psychological or social problems, including sleep problems, and at least 25% received a symptom diagnosis. Changes in pain and fatigue during similar time intervals appeared to be directly associated.

Only few symptom diagnoses other than fatigue were made during the first consultation. This could reflect variation in symptoms experienced by patients, but possibly also the tendency of the GP to record one main symptom. However, at baseline, patients reported on average 4 out of 13 listed symptoms to be present since their fatigue started (IPQ-R), and on average 3 symptoms to be associated with their fatigue. Twenty-nine percent of patients reported 'quite a lot' to 'severe' pain at baseline, and 26% reported substantial limitations in activity due to their pain (SF-36).

Both the diversity and the frequency of diagnoses seem to be in line with overviews of diagnoses for fatigue[1-3], and literature on multiple symptoms co-occurring with fatigue, indicating that in fatigued patients multiple organ systems in the body may be involved. The relatively small proportion of recorded somatic pathology is in line with findings from smaller studies.[4,5] The number of diagnoses representing psychological or social problems is larger than the average of 9% found in a national survey in Dutch general practice(6), but may still be an underestimation considering the results from the questionnaires, which showed a much higher proportion of elevated scores of distress (61%), depression (24%) and sleep problems (65%). Additionally, a majority of patients (57%) (partly) attributed their fatigue to stress. Other studies have also shown that psychological symptoms or conditions registered in the medical records are an underestimation of the prevalence of such symptoms[7,8], even among frequent attenders.[9] This may in part be due to the presentation of somatic symptoms only[7]; alternatively, in many cases GPs either may not recognize or may not discuss patient's stress or worry[10], or they may not record it, despite discussing the problems.

(Medically) explained fatigue

Half of the participants in our cohort received a diagnosis that could possibly or plausibly explain their fatigue. Establishing whether the diagnoses we retrieved from the records could provide an explanation for the presented fatigue proved to be difficult without a more complete picture of the patient's medical history and (severity of) additional symptoms. Also, our focus was on diagnoses rather than on individual patients, who may receive multiple diagnoses that possibly explain their fatigue. A consequence of our strategy is that we could not establish in how many cases the fatigue remained 'unexplained'; this would (also) require the opinion of the individual GP. In contrast to our observational study, many previous studies on fatigue have included patients with 'unexplained' fatigue. However, even in these studies the extent to which psychological or social factors may play a role is often not clear and the definition of 'medically unexplained (physical) symptoms' (MUPs) is subject to debate.[11-13] Conversely, even when an explanatory diagnosis is established, the aetiology of fatigue remains largely unknown. Whether or not patients receive an explanatory diagnosis, co-occurring symptoms and the consequences of fatigue in daily life are important. Fatigue is a disabling and multidimensional symptom in many diagnosed conditions, and increasing attention is given to management of the fatigue itself.[14-16]

Existing comorbidity

Fatigue presented in primary care may (in part) be a manifestation of an existing chronic condition. According to our definition, which was limited to diseases that could be assumed to be present regardless of treatment or date of diagnosis, 11% of 571 participants had a chronic disease, while on average 20% of 642 participants reported having a chronic disease in the patient questionnaires. Unfortunately, we did not ask patients what disease they had, and ultimately we did not have sufficient information from the medical records to assess whether conditions such as back pain, thyroid dysfunction or depression, were current at the time of consultation.

Additionally, we do not know the number and combination of existing chronic conditions in individual patients, and eventually the total sum of existing and new diagnoses during follow-up. Part of the new diagnoses may have been an exacerbation or new recording of an already existing condition not included in our strict definition of existing co-morbidity. Information on total number of diagnoses may be useful, since community studies have reported that the number of chronic conditions is related to fatigue[17] more than the type of condition.[18] More general characteristics of a condition such as severity, duration, and accompanying limitations vary substantially within conditions and may be more strongly associated with fatigue than the type of condition.[18] This may explain the difficulties that we encountered when assessing diagnoses as potential explanations for fatigue.

Diagnostic tests

In our study the GP performed diagnostic tests in most cases (88%), and fatigue was often the only reason for performing diagnostic tests. Fatigue accounts for a high percentage of diagnostic testing in primary care[19], and our results are comparable to the 83% reported in a study of 59 patients presenting with fatigue in primary care.[20] The discrepancy between the high frequency of testing and the low rate of pathology is in line with other studies, showing that the diagnostic yield of tests conducted in patients with fatigue is low[20-23], which justifies the recommendation to initially postpone testing in the Dutch guideline for diagnostic testing in cases of unexplained symptoms.[24] Diagnostic testing may also be used as a management strategy rather than for indicated reasons, and GPs may implicitly perceive pressure from patients to request tests.[25] This may have been the case in our study, as GPs indicated that a request of the patient was a reason for diagnostic testing in 24% of cases, and the wish for testing was a reason to consult for a majority of patients.

Pathology versus dysfunctional physiology

Today in medical education and practice the biopsychosocial model is taught and accepted, but the use of classifications based on the traditional biomedical model, placing psychological and social factors in a different category apart from somatic problems is common in daily practice.[26] While the (ICPC) classification system in primary care provides an elaborate range of diagnostic categories, including symptom diagnoses, the forced choice for one (main) diagnostic category may complicate the recording of complex problems such as fatigue, which are difficult to allocate to specific codes.

In the absence of clinical disease symptoms may still indicate a dysfunction in (psycho)physiology. Taking dysfunctional physiology into account next to definite pathology may provide a bridge between biological and psychological dimensions, since the *interactions* of these different processes may result in symptoms. Williams et al (therefore) propose to consider both pathology and abnormal (psycho)physiology in daily practice.[26] Several others have also suggested that a shift in focus from identifying one cause for symptoms to (dys)functioning of common physiology would be more fruitful[27-29], and new propositions for terminology and classification have been made[27,30,31] that may be more practical in the assessment of fatigue and its consequences for patients.

Functioning may be assessed at different levels. Impairment of bodily functions (or structure) may be seen as a micro dimension of dysfunctioning besides limitations in daily activity or (social) participation. These three dimensions of functioning or disability are part of a model proposed by the World Health Organisation, that may be useful in the investigation of multidimensional symptoms such as fatigue[32]. The interrelations

between (impairments of) bodily and psychological functions, health behaviours and social relationships have become evident from physiological research[33], and are supported by the prognostic outcomes of our study.

Fatigue in primary care: course and prognostic factors

Participants in our cohort showed a variable course of fatigue, with a small minority showing a fast recovery and a minority reporting persistent fatigue. Fatigue was associated with sleep problems, psychological symptoms, and functional limitations. In our review we found 30-50% recovery after six to twelve months based on four smaller studies among patients presenting with fatigue in primary care. Half of the patients in our study showed recovery after one year. In contrast to previous studies, our definition of fatigue outcome was based on a combination of several repeated measurements. Using this definition, distinct patterns in the course over the year could be distinguished, which appeared to be consistent with functional outcomes and other symptoms.

Duration of fatigue and time of consultation
The one-year follow-up started shortly after the time of consultation for fatigue. However, the episode of fatigue has started some time before the patient decided to consult the GP. Most of our participants were already fatigued for at least 6 months when they consulted their GP, and 40% even for at least one year. In line with this, a majority of participants (67%) indicated a long duration of fatigue as a reason to consult. Many patients who were chronically fatigued at baseline (i.e. at least six months) showed a chronic course during follow-up.

Since we instructed the GPs to include patients with a new episode of fatigue, we did not expect to include such a large number of chronically fatigued patients. Several explanations may clarify this high percentage.
Response bias may have played a role. Although the response rate was high (75% of provisionally enrolled patients), improvement of fatigue was a frequently mentioned reason for non-participation. These patients might have had a shorter duration of fatigue. A short duration may also have been a reason to be less motivated to participate among those who indicated to have no time or interest, or for others who did not provide a reason.
Secondly, it is possible that not all GPs strictly adhered to the new episode-criterium. Our results during follow-up showed that fatigue may have a fluctuating course. Additionally, the new-episode criterion implied quite some recall for both (the busy) GP and (the fatigued) patient. If the patient had consulted with a main symptom of fatigue for more than six months before, the GP, and consequently the patient, must have

verified whether that fatigue had been resolved in the meantime. It may be difficult for patients and all the more for GPs, to distinguish between a new episode and ongoing fatigue: fluctuations may be regarded as part of the same episode, or alternatively as a new episode. Therefore, it may be possible that our study population is not strictly composed of patients with a new episode of fatigue. Our results, however, do seem to indicate that a majority of patients who consult for fatigue do not visit their GP until, and because, they are chronically fatigued.

Demands and resources

We used two separate prognostic models to investigate which factors are important predictors of the course of fatigue: we compared two ends of the prognostic range - both favourable and unfavourable outcome - with a more heterogenous group that also included patients with a fluctuating course. This allowed a more specific focus on either good or poor outcome than using one model only.

The picture emerging from the two different models suggests an imbalance between perceived demands or burden and resources in patients with a poor outcome. In predicting a fast recovery, better perceived health contributed to outcome, which may reflect better resources. Perceived demands also seemed to be important, with less perceived difficulties and not caring for others favouring a good outcome. Male rather than female gender added to a fast recovery in this model as well. This seems to correspond with several psychosocial differences between men and women reported in the baseline questionnaire. In line with a previous study[34], women more often attributed their fatigue to family problems or worries. Although the total number of work hours (including paid and unpaid work) did not remain a predictor in the final model, women more often reported doing unpaid work every day, and more often reported this in combination with a paid job. Women also attributed fatigue more often to their emotional state and reported more physical symptoms, elevated levels of distress, and higher levels of fatigue.

Less social support contributed to a chronic course, and might reflect a lack of resources. Possibly, less perceived demands may be initially important in the prediction of a fast recovery, with a lack of resources becoming more important in prediction of a more chronic outcome. Alternatively, both sides of the balance are interrelated, and more perceived demands – with persisting symptoms – may inherently result in a perceived lack of resources and a need for more support. Our results are in line with outcomes of a qualitative study on fatigue among healthy employees, reporting care-taking responsibilities, stress and overwork as main causes of fatigue, and a positive influence of support.[35]

Patient expectations

Negative expectations of the course of fatigue contributed both to a chronic course and inversely to a fast recovery. The predictive value of expectations of a long-lasting course on fatigue after six months was also reported in a RCT among 129 fatigued primary care patients.[36] Likewise, perceptions of a chronic course of symptoms may contribute to a poor prognosis of pain[37], physical and mental health in general (38), and important in this regard, such perceptions also proved to be a strong predictor of GP consultation in patients presenting with a new health problem.[39] Conversely, expectations of improvement were associated with positive health outcomes in several (prognostic) studies[40,41], and both positive and negative expectations may affect outcomes of treatment.[42]

The strong predictive value of these perceptions raises questions about who were having such perceptions, and why. We measured expectations with a subscale composed of 5 questions, ranging from 'fatigue will last a short time' to 'expect to remain fatigued for the rest of my life'. One-third of patients agreed with 'fatigue will last a long time'. In a cross-sectional pilot study a similar percentage of patients presenting with fatigue (35% of 113) reported that they sometimes thought that their fatigue would never resolve (unpublished results).

Perceptions of the course could be related to insight into causes and aggravating or relieving factors of fatigue, and perceived possibilities of being able to actively influence such factors or the fatigue itself. Baseline scores of negative expectations were indeed inversely correlated with personal control and insight in the symptom. In a qualitative study[37], knowing one is healthy and fatigue is temporary was a relieving thought, and a sense of control was linked to fatigue being acute rather than chronic. The authors suggest that a lack of control may not only switch one's perception of fatigue from acute to chronic but also from being healthy to being ill, resulting in doctor visits.[35] In a study among CFS patients, showing similar inverse correlations between perceived control of symptoms and negative expectations regarding the course, such expectations were also associated with beliefs that health is determined by doctors and with giving up any effort to cope with the illness.[43]

Having a current chronic disease may also account for negative expectations of the course of fatigue. Patients with a chronic disease according to our definition did not show a significantly higher score on negative expectations, but as mentioned before, our definition of co-morbidity was not all-inclusive.

Additional potential prognostic factors

In this study we have investigated a wide range of prognostic factors. We did not include specific work-related factors, but these have been studied extensively in a large cohort study among employees.[44] The results partly indicate that work-related factors may be more important in the onset of fatigue than its prognosis. However, apart from perceived health and psychological attributions, (changes in) several work-related factors contributed to the course of fatigue, including decision latitude, psychological job demands, conflicts with colleagues and social support at work.[44-46] Our findings, although not measured in the context of work, reflect that similar concepts are important, including perceptions regarding health and fatigue, perceived demands or difficulties and social support.

Because of practical reasons we did not include all potentially relevant prognostic factors: adding more questions to the extensive baseline patient questionnaire would increase the burden on participants to complete it, and probably decrease the response rate. Nevertheless, several other factors may be worthwhile to study in future, as they may be related to outcome of fatigue or interact with important prognostic factors, such as patients' expectations of the course of fatigue.

Fatigue appears to be perceived differently between cultures[47], and perceptions regarding the course of fatigue may also be shaped by sociocultural factors. In a comparative study, British patients had more negative perceptions of the course of their fatigue than Brazilian patients.[48] As our study was performed in the Netherlands only, the contribution of specific sociocultural factors to the course of fatigue would have been difficult to measure, despite its multicultural society. We did not inquire about ethnic background and participation was restricted to patients with sufficient knowledge of the Dutch language, further limiting the possibilities to study the influence of cultural background on fatigue.

Spiritual beliefs, which can be related to religion and culture, may also be related to the perception of symptoms[49] are considered part of the healing process[50-52] and may contribute to improvement of symptoms.[53] Whereas attention to spiritual factors in medical practice, training and research has mostly been confined to palliative care, patients with chronic pain and fatigue may also turn to spirituality as a resource for dealing with their symptoms.[54,55] The assessment of this dimension in health care may be complicated, as it may be seen as a personal coping mechanism that remains a private concern of the patient[23], and as a personal experience – like fatigue – it may be regarded (as) intangible. However, suggestions have been made to expand Engel's biopsychosocial model to a biopsychosocial-spiritual model[56], and factors such as search for meaning and purpose, inner peace, resilience, sense of connection, duties and life

choices, may put many factors that are already in the biopsychosocial model in wider perspective. Such aspects may be reflected in perceptions including causal attributions, expectations and personal control; coping; lifestyle; social support; caring for others and prolonged difficulties, many of which were prognostic factors in our analyses. A related factor is acceptance, as opposed to attempting to control symptoms, which was associated with well-being and less fatigue in patients with CFS[57] and with better outcomes in chronic pain patients.[58]

Lifestyle may be associated with both perceptions and prognosis of fatigue and comprises many factors. Although we did assess physical activity, smoking and drinking habits, we did not (extensively) assess diet and relaxation, which are considered as part of the 'big five' of important lifestyle factors. Despite their importance, defining and measuring these factors may be complicated in a prognostic study next to many other potential prognostic factors, and therefore complicates analysis of their contribution to the course of fatigue. The relevance of lifestyle factors may be more clearly assessed in an explanatory design such as an intervention study, focusing on the effect of a specified healthy diet or relaxation techniques. We did assess the prognostic value of physical activity, but did not find an effect in multivariate analyses. However, the contribution of this factor (in fatigued patients) may not be straightforward. Studies on CFS suggest that different patterns of activity – both inactivity and bursts of activity – have unfavourable effects, while a gradual increase in activity seems to be the optimal strategy[59]; effects of graded exercise therapy are still being investigated.[60] Lifestyle factors may be interrelated and it is probable that their predictive value largely depends on patterns in time rather than linear frequency; this complicates an evaluation of their contribution to fatigue outcome.

Management and treatment

Treatment for fatigue or other conditions that could account for the fatigue, could influence its course. Patients' self-report after the consultation indicated that one third of patients received treatment, more often for another reason than fatigue. This suggests that most of the treatment patients received was more directly related to established diagnoses. Because our aim was to perform an observational study, we were not able to assess treatment effects, and we did not explicitly ask GPs to report their management. Relying on medical records for a description of the management strategies GPs employed when patients visited for fatigue would probably not cover all management in many cases, such as whether and what advice was given.

Consulting the GP for fatigue
When interpreting the results of the prognostic analysis, it should be kept in mind that these data were collected *after* the consultation. Expectations of the course may in part be altered by the GP's management and communication. It has been suggested that if people with symptoms visit their GP, their concerns or expectations may be as important as their symptoms.[61]

Most patients reported to be satisfied with the way their GP managed their complaint. Although we did not assess the predictive value of patient satisfaction or reasons to consult the GP, it would be interesting to know whether patients who were dissatisfied with management or who indicated a wish for treatment (21%) or advice (36%) had different outcomes. Descriptive analysis showed that outcomes seemed less favourable for patients who had a wish for treatment compared to those without (8% vs 20% showing a fast recovery and 44% vs 21% showing a chronic course).

Course of fatigue and clinical outcomes

Influence of medication
Fatigue is a listed potential side effect of several frequently used medicines. In a random sample of 272 patients from our cohort, only four cases side effects of medication could have contributed to cause the fatigue that was presented to the GP: in these cases the duration of the fatigue was shorter than the duration of medication use (unpublished data). However, 20% of patients in this subsample were prescribed medication with fatigue as a listed potential side-effect, which could have exacerbated the fatigue that patients presented to the GP. Considering our relatively young population, this number could have been an underestimation, as older people have more comorbidity and are more often diagnosed with medication side-effects after presenting with fatigue.[62] We did take account of the substantial fatiguing side-effects of chemo or radio therapy a priori by excluding patients receiving such treatment. Furthermore, in six cases side-effects were recorded in the medical records as new diagnoses; the nature and relation to fatigue in these cases was not clear.

Fatigue and (co)morbidity
Clinical diagnoses and the course of fatigue are two different outcomes that were recorded, collected and analysed separately in this study. Combining both outcomes might have clarified the results in both ways. However, in order to establish associations between the course of fatigue and established diagnoses, information on duration and severity of disease or illness episodes would be required, which is difficult to determine from medical records. Apart from this, to provide reliable answers to this question,

collection of these data should be planned correspondingly in a prospective way; by asking the GP to report fatigue status when reporting diagnoses during follow-up, and possibly also by asking patients to report any new diagnoses when completing follow-up questionnaires on fatigue status. Practical reminders such as a pop-up screen in the GP's computer for study participants could be deployed, but such adaptations might compromise an observational design.

Although the potential impact of diagnosis on outcome has not been adequately assessed, receiving a syndrome label for fatigue may influence outcome[63], arguably predicting either a more or less favourable outcome, as it may generate acceptance, but also reinforce the sick role and pessimistic beliefs about the course of fatigue.[64] In our study, only four patients received a diagnosis of CFS, and a small minority received another functional syndrome diagnosis at some time before, or during the year after the consultation. Receiving any diagnosis may affect prognosis, either through modifying expectations, beliefs or attitudes, or through a change in management of the problem by the GP.

Methodological considerations

Defining fatigue outcome

Our inclusion criterion of fatigue presented as a main symptom, without selection based on severity, allowed our study to be as practice-based as possible. We did base our outcome on questionnaires, which may remain more difficult to translate to practice compared to a single question about the current status of symptoms. However, the use of validated questionnaires may reduce the risk of information bias and facilitates comparison of outcomes with other studies. We used dichotomised scores to define subgroups and outcomes, using a cut-off that has been used previously in fatigued populations. The selection of any cut-off remains an arbitrary choice, but the combination of several repeated measurements in defining outcome has probably contributed to a more accurate measure.

The impact of fatigue on daily functioning, or experienced burden may also be a useful and perhaps more practical indication of fatigue severity.[61,65] Although we did not use this as outcome measure, the similar patterns in the course of both fatigue and (limited) functioning suggest a clear impact of fatigue, although this association may work both ways. We did measure impact of fatigue with the IPQ-R Consequences scale at baseline. On this scale containing 5 items, 35% of patients indicated that their fatigue had large consequences for their life; this percentage was 19% in patients with a favourable course vs. 43% in the group with an unfavourable course.

Hawthorne effect

A potential source of bias is the effect of participating in a study, known as the Hawthorne effect. Although an inherent part of every prospective study, it should be taken into account when interpreting results. Participating in our study required completing an elaborate questionnaire after the consultation, and several more during follow-up. This allowed for more time and attention to consider the nature and severity of symptoms and other related factors than a consultation in primary care would provide. This will have provided participants with more insight into their symptoms, as was mentioned by some participants, and may have resulted in a better outcome – although the increased attention may also have worsened their symptoms. A similar 'intervention effect' may have influenced the GP and thereby the content of the consultation; GPs may have regarded the Fatigue study as a useful and possibly time-saving management tool. This may have affected the GP's management, but is unlikely to have influenced the range or number of diagnoses.

External validity

Demographic characteristics of the study population may give an indication of the generalisability of our results. The participating practices, to start with, can be considered to be representative of Dutch general practice, as they included urban, rural, solo and collective practices. The GPs enrolled on average five patients (range 1-30 per GP), which seems low considering the prevalence of fatigue as a presenting symptom. Although we instructed the GPs to include consecutive eligible patients and made regular efforts to remind them of the study, as in most (epidemiological) studies 'Lasagna's law' may have resulted in a large difference between potentially eligible and actual numbers of enrolled patients.[66]

Although older people may regard fatigue as an inherent part of old age and less often mention it when visiting the GP, compared to a survey in primary care, relatively few older people were included in our study.[67] Our results may therefore be less representative for older patients with a main symptom of fatigue. This probably affects the range of existing co-morbidity and new diagnoses that we retrieved, and possibly the outcomes and predictors in our prognostic models.

The finding that the majority of our population were women is not surprising as it corresponds with data from other studies among patients presenting with fatigue in primary care. Compared to population statistics, in our sample a smaller number of patients had higher education (18% vs. 25%), and a larger number was employed (77% vs 63%).[68] Furthermore, a majority of participants already had chronic fatigue at baseline, which corresponds with previous smaller studies among patients presenting with a main symptom of fatigue.[69-71]

Based on the available data, improvement of fatigue was more often a reason for non-response than being too tired. It is therefore possible that participants in our study had

more severe fatigue than nonresponders. The lack of data for 40% of non-responders limits a more thorough assessment of selection bias.

Study implications and recommendations

The results and limitations of our study, in combination with the work of others and the gaps in research on some issues bear several suggestions for further research and clinical practice.

Implications for clinical practice

Many patients consulted with an episode of chronic rather than recent fatigue, and the co-occurring symptoms and limitations in functioning showed similar patterns. The course of fatigue was highly variable and associated with various factors, including perceptions and social factors. Exploring the status of associated symptoms and functioning when patients present with fatigue would give more insight into the severity of the problem and may give directions for tailored advice. History taking for patients presenting with fatigue should include the patient's perceptions regarding their symptom(s), and origins of negative expectations, in order to help patients adjust incorrect or ineffective perceptions.

Next to diagnosis and specific treatment strategies, good communication is an essential part of medical care of (medically unexplained) symptoms.[72] The implications of our results seem to relate primarily to this part of care. Others have shown that a clear and optimistic communication style seems helpful, unless patients have negative emotions at the start of the consultation[73]; reassurance of patients may exacerbate symptoms if specific concerns are not addressed.[74] Our prognostic models suggest that the GP should notice and acknowledge patient perceptions regarding their fatigue, and changes in perceived burden and resources. This may require more attention to patients' (underlying) concerns which are often not explicitly presented[75], while making patients feel free to talk about their problems has been ranked a major priority in primary care provision.[76] A recent study into key components of cognitive behavioural therapy and counselling revealed that emotional processing, including the expression, acknowledgement and acceptance of emotional distress, was a key predictor of good fatigue outcome.[77] In routine consultations, the GP's attitude may already facilitate or complicate exploration and resolution of psychological problems.[78] These findings underscore the importance of patient-oriented communication.

Further research: diagnosis and prognosis

Future diagnostic studies on fatigue in primary care should include the GP's and patient's opinion to facilitate assessment of the 'explanatory value' of diagnoses for presented fatigue. It would also be useful to compare such outcomes with initial attributions for fatigue of both patients and GPs. Additionally, studies on patients presenting with fatigue should not exclude patients with co-morbidity at baseline, but include a prospective assessment of all current diseases or conditions and, ideally, take account of multiple morbidity in relation to fatigue during follow-up.

Prognostic studies should include repeated measurements of fatigue and potentially associated outcomes such as sleep, perceptions and (psychological) symptoms in order to study temporal associations with fatigue. While similar (stress-related) dysfunction of physiological pathways has been suggested to play a role in symptoms including both fatigue and pain[79-82], epidemiological studies on longitudinal associations are scarce. We made a first step by investigating the temporal relations between pain and fatigue. Furthermore, repeated questions on which factors worsen or alleviate fatigue could provide more insight into helpful self-management strategies and patients' own insight in (un)succesful coping.

Limiting inclusion of participants to those with a limited duration of fatigue would enable studying prognostic factors that are important in the prevention of a chronic course. However, as many patients consulting with fatigue have been tired for a long time, this does not seem to reflect daily practice, and would not seem feasible. Conversely, unless the aim is to study further prognosis of chronic fatigue, inclusion of participants in prognostic studies should not be restricted to patients reporting chronic fatigue at baseline.

Integration and collaboration between different disciplines and levels of research – epidemiology, (psycho)physiology and qualitative research - could possibly yield more insight in the (causal) associations of various somatic, psychological or social factors with the outcome of fatigue. This could be established by combining different research methods – for example in an intervention study – by evaluating the effectiveness of tailored interventions based on assessment of prognostic factors at baseline; by measuring neuroendocrine parameters in patients with different outcomes of fatigue; or by using qualitative research methods to explore factors to which patients attribute their recovery.

Further research: interventions and management

Currently, there are no evidence-based guidelines for the management of fatigue in primary care, and there is no evidence for primary care intervention programmes. In the NICE guideline (UK) on CFS, recommendations after diagnosis are to 'manage symptoms as usual', with additional suggestions made for interventions aimed at improving lifestyle (management of sleep, balancing rest periods, relaxation, diet and physical activity).[83] Intervention studies could investigate the effects of an active management strategy that addresses perceptions of fatigue, other symptoms, and the consequences of fatigue for patients. A multidimensional (tailored) strategy may be most effective in decreasing symptoms and empowering patients to self-manage their fatigue. This may include keeping a diary of symptoms, coping and related perceptions. Because of its continuity, general practice has been suggested a suitable setting for allowing a process that initiates reflection in patients.[84]

The results of our study underline the importance of perceptions in the prognosis of fatigue. Modification of thoughts and beliefs about symptoms is an essential part of cognitive behavioural therapy (CBT), which has been studied in selected fatigued populations, mainly in patients with CFS. Although diagnosing CFS and subsequently managing these patients is not common practice in primary care[85,86], the results of these intervention studies may be useful for a larger group of fatigued patients. However, despite the research attention for CFS, high quality evidence of interventions is still lacking.[87]

Few studies have investigated the effectiveness of CBT on secondary outcomes, with inconclusive results on psychological symptoms and no effects on physical functioning[87]; one study showed positive effects on pain levels.[88] Considering the associations between fatigue, daily functioning, sleep, pain and other physical and psychological symptoms, future trials on interventions for fatigue should assess these secondary outcomes as well. Alternatively, given the diverse target populations of interventions such as CBT[89], study populations may even be broader including patients with different combinations of (unexplained) symptoms. Selection of participants may then be based on symptom perceptions such as negative expectations, rather than on symptoms alone. Study outcomes may also be tailored to the problems or symptoms that patients (most) wish to improve.

Given the nonspecific and multidimensional nature of the symptom, new intervention methods that take both body and mind into account should be studied in patients presenting with (chronic) fatigue. Suggestions have already been made to combine CBT with other interventions to increase treatment effectiveness.[87] Furthermore, Bakal et al point out the limitations of CBT in failing to address the psychobiology of the symptom experience, and argue that incorporation of somatic awareness in the clinical care for

patients with MUPs or 'bodily distress' would be helpful in changing illness beliefs and behavioural responses to symptoms.[27] Recent recommendations for management of patients with MUPs include integrating physical and psychological explanations that avoid blame and provide an opportunity for self-management.[90] Finally, mindfulness-based stress reduction or –cognitive therapy is a recent approach based on meditative observation and acceptance of thoughts, emotions and (bodily) sensations without judgment or reactivity. Mindfulness has been studied mainly in patients with psychiatric symptoms, but may also be effective in improving fatigue and related outcomes.[91,92] Interventions that take psychosocial factors into account and are helpful in improving fatigue may also supplement medical management aimed at co-existing disease or physical symptoms.

Conclusion

The results of this study show that the course of fatigue is unfavourable in many patients presenting with fatigue. The results also confirm that fatigue is associated with limitations in functioning, and that many different factors may play a role in the course and prognosis, including physiological, psychological and social factors. These factors may not all be directly measurable, visible and 'diagnosable' for the GP, but do have a large impact. GPs should therefore explore perceptions, associated problems, symptoms and functioning when patients present with fatigue.

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Whether you challenge the challenge or you give in to the challenge, that is what decides your spirituality. Is your spirit higher than the challenge so you can face it? // Spirituality is facing yourself with a smile when life confronts you. *Yogi Bhajan*

Summary

This thesis is focused on fatigue as a main symptom presented in primary care. In **chapter 1**, the subject of fatigue in primary care is briefly introduced, followed by the background and **aims** of our study. We performed a prospective cohort study among adult patients visiting their GP with symptoms of fatigue, to answer questions on the course of fatigue and associated problems, prognostic factors and diagnoses within one year after presentation.

In **chapter 2**, the results of our question on **diagnoses** are presented. While many studies have focused on 'unexplained' fatigue, little is known about the distribution of diagnoses that account for fatigue presented in primary care. We aimed to describe the diagnoses established within one year after the consultation that are likely to explain fatigue presented as a main symptom in primary care. Diagnoses were evaluated on the possibility of an association with presented fatigue, in a Delphi procedure and by GP expert opinion. After initial content-based evaluation, diagnoses were also evaluated by taking into account the time period between onset of fatigue and establishment of diagnosis. For 571 patients, data on diagnoses were available. One-fourth of these patients received a diagnosis that provided a plausible explanation for their fatigue; these diagnoses included both psychological problems (16%) and somatic diseases (8%). About one fifth of patients received symptom diagnoses, most often musculoskeletal problems, that could possibly explain the fatigue but for which there was no consensus regarding a plausible explanation of the presented fatigue. Except for infections, considering the time period between onset of fatigue and establishment of diagnoses in the assessment of a plausible explanation proved to be difficult because of insufficient clinical information. The results do show that a minority of patients were diagnosed with serious pathology, and most patients did not receive a diagnosis that clearly explained their fatigue. However, considering the results of self-reported psychosocial problems, including sleep, the recording of such diagnoses by GPs seems to be an underestimation. The wide range of the conditions and symptoms that may explain or co-occur with fatigue indicate that it is a multidimensional problem that deserves attention not only as a symptom of underlying specific disease.

To summarize the available evidence on the course and prognostic factors of fatigue, we conducted a **systematic review** in both primary care patients and in the community. The results are presented in **chapter 3**. Two reviewers independently screened identified citations, discussed eligible studies, and assessed the methodological quality of selected studies. Data concerning study population, duration of follow-up, measurement of fatigue, outcome, and prognostic factors were extracted. Studies with populations selected by a specific disease or postpartum condition were excluded. We selected 21 articles reporting on 11 (partly) primary care cohorts and six community cohorts. Follow-up was up to 1 year in primary care and up to 4 years in the community,

and in most studies that presented duration of fatigue, participants were chronically fatigued. Because of the wide heterogeneity of studies, a qualitative analysis was performed. Recovery of fatigue varied widely, but no differences were found between settings. Sufficient evidence for an association with recovery was found for lower severity of fatigue, and limited evidence was found for good self-reported health, mental health, and psychological attributions. A major shortcoming in methodological quality of most studies was a potential bias due to a lack of information on response or loss to follow-up. Most studies on fatigue included patients with long symptom duration at baseline, which renders studying prognosis early in the course of fatigue impossible. We therefore conclude that prognostic studies should use an optimal design including selection of an inception cohort with limited duration of fatigue at baseline, a sufficient sample size, and information on rates and selectivity of response and loss to follow-up.

In **chapter 4**, we describe the results of our cohort study on the **course** of fatigue, functioning and associated symptoms. We performed an observational cohort study in 147 primary care practices. Patients consulting their general practitioner for a new episode of fatigue were sent questionnaires at 1, 4, 8, and 12 months after baseline. We collected measures of fatigue, perceived health and functioning, absenteeism, psychological symptoms, and sleep using the Checklist Individual Strength, the 36-Item Short Form Health Survey, the Four-Dimensional Symptoms Questionnaire, and the Pittsburgh Sleep Questionnaire Inventory. Of 856 recruited patients, 642 were enrolled in the study (response rate 75%). Completion rates during follow-up ranged between 82% and 88%. Patients were classified into 4 subgroups based on fatigue severity scores over time. We assessed patterns in the course of all outcomes in these subgroups and in the total population, and tested changes over time and differences between subgroups. For 75% of enrolled patients, four distinct groups could be discerned: 26% of patients had continuously high scores for fatigue, 17% had a fast recovery, 25% had a slow recovery, and 32% initially improved but then had a recurrence of fatigue. Patterns for the secondary outcomes of symptoms and functioning were all similar to the pattern for fatigue within each of the subgroups. The findings of this study suggest a longitudinal relationship between the severity of fatigue, impaired functioning, psychological symptoms, and poor sleep. Based on our results, we recommend physicians to be aware that a substantial proportion of patients seeking care for fatigue have these additional health and psychosocial problems.

In **chapter 5**, we show the results of a prediction analysis of **prognostic factors** of the course of fatigue in our cohort. Our aim was to determine which combination of factors was most strongly associated with a favourable or unfavourable outcome when patients presented with fatigue as a main symptom in primary care. The prognostic value of potential predictors was assessed by applying multivariable logistic regression analysis.

The outcome was severity of fatigue, defined as a combination of dichotomised scores on several repeated measurements with the Checklist Individual Strength. Two separate models were used to predict either a favourable or an unfavourable course of fatigue. Baseline severity of fatigue and patient expectations of chronicity consistently predicted a poor outcome. Additional factors predicting a chronic course were baseline pain intensity and less social support. Baseline characteristics predicting a fast recovery were: male sex, not providing care for others (for example, for older people), better perceived health, and fewer (serious) prolonged difficulties. Both models had good reliability and discriminative validity. The identified combination of predictors reflects the biological, psychological and social dimensions of fatigue, with a significant contribution of patient expectations of chronicity in the prediction of a poor prognosis. We conclude that these negative perceptions, which are modifiable, should receive more attention in the initial assessment of patients presenting with fatigue.

In **chapter 6** we focus on the temporal relationship between fatigue and **pain**. So far, most studies on the association between pain and fatigue have used cross-sectional data. Pain was measured using the Short-Form health survey (SF-36) and fatigue using the severity scale of the Checklist Individual Strength (CIS). Longitudinal associations were analysed using generalized estimated equations (GEE). We used three different models assessing possible relationships between the symptoms in time, either in the same intervals or with a time-lag, suggesting either a synchronous association or temporal association. The regression coefficients were strongest in the model assessing synchronous change, indicating that a one-point improvement in pain was associated with a 0.25 improvement in fatigue in the same time interval (adjusted for potential confounding). Baseline duration of fatigue and expectations of its future course significantly modified the association in this model, with stronger associations between changes in pain and fatigue found in patients with a shorter duration of fatigue or more positive expectations. The results indicate that changes in pain and fatigue are directly related in time, rather than showing temporal associations.

In the final **discussion** chapter, the results of our studies are discussed in relation to each other and the literature. Some methodological issues are considered, and suggestions for future research and practice are made. We conclude that many different factors may play a role in patients presenting with fatigue, including perceptions, pain and psychosocial problems. The identification of patients with a poor prognosis may therefore require more exploration by the GP.

Samenvatting

Dit proefschrift gaat over moeheid bij mensen die dit als belangrijkste klacht presenteren tijdens een bezoek aan de huisarts. In **hoofdstuk 1** wordt het onderwerp moeheid in de huisartspraktijk kort geïntroduceerd, gevolgd door de achtergrond en **doelstellingen** van het onderzoek. We wilden een antwoord krijgen op vragen naar het beloop van de moeheid in relatie tot functioneren en andere klachten, factoren die het beloop voorspellen en diagnosen die werden gesteld binnen een jaar na het consult.

Om deze vragen te kunnen beantwoorden hebben we een cohortonderzoek uitgevoerd bij volwassen patiënten die hun huisarts bezoeken met de klacht moeheid. In totaal hebben huisartsen uit 147 praktijken binnen anderhalf jaar 856 patiënten aangemeld. Van deze mensen hebben er 642 (75%) toestemming gegeven voor deelname en thuis na het consult de eerste vragenlijst ingevuld. Daarna kregen deelnemers aan het onderzoek na 1, 4, 8, en 12 maanden nog een (kortere) vragenlijst. Deze vervolglijsten werden ingevuld door 82 tot 88% van de deelnemers. Gegevens uit medische dossiers werden opgevraagd bij de deelnemende praktijken. Van 571 patiënten waren gegevens beschikbaar over de diagnosen die huisartsen hadden gesteld. In hoofdstuk 2, 4 en 5 worden de resultaten gepresenteerd voor de vragen over gestelde diagnosen, het beloop en voorspellende factoren van het beloop van moeheid.

In **hoofdstuk 2** beschrijven we welke **diagnosen** zijn vastgesteld binnen een jaar na het consult voor moeheid, die de moeheid mogelijk kunnen verklaren. Hoewel er veel onderzoek is gedaan naar 'onverklaarde moeheid', is er weinig bekend over de verdeling van diagnosen die moeheid kunnen verklaren die als klacht bij de huisarts wordt gepresenteerd. Eerst zijn uit alle diagnosen die in het dossier waren vermeld, de diagnosen die de moeheid zouden kunnen verklaren geselecteerd. Daarna is gekeken naar de tijdsduur tussen het begin van de moeheid en het stellen van de diagnose. Afhankelijk van de diagnose, kan het voor het beoordelen van een mogelijk verband met de moeheid veel verschil uitmaken of de diagnose meteen of vlak na het consult is gesteld, of bijvoorbeeld na een (half) jaar, en hoe lang de patiënt al moe was op het moment van het consult.
De helft van de 571 patiënten kreeg een diagnose die de moeheid zou kunnen verklaren. Bij deze diagnosen waren bijna alle classificatiegroepen op basis van ziekte of orgaansysteem zoals gebruikt in de huisartsgeneeskunde vertegenwoordigd. Een vijfde van de patiënten kreeg een symptoomdiagnose, meestal van klachten van het bewegingsapparaat. Zestien procent van de patiënten kreeg een psychische diagnose, en een minderheid van 8% had een lichamelijke ziekte. Behalve voor infecties, bleek het lastig om vast te stellen welke tijdsduur tussen het begin van de moeheid en het vaststellen van de diagnose relevant was bij het bepalen of een diagnose de moeheid zou kunnen verklaren. Hiervoor zou meer klinische informatie nodig zijn, bijvoorbeeld over de ernst en duur van de vastgestelde ziekte of andere klachten. Wat we kunnen

concluderen is dat bij een minderheid van de patiënten een ernstige ziekte werd vastgesteld, en dat tenminste de helft van de patiënten geen diagnose kreeg die de moeheid zou kunnen verklaren. Echter, gezien de resultaten uit de vragenlijsten lijkt er een onderregistratie te zijn van psychosociale diagnosen, waaronder slaapproblemen. De grote variatie in lichamelijke en psychische aandoeningen en klachten bij mensen met de klacht moeheid geeft aan dat het een probleem is met veel verschillende dimensies. Dit geeft aan dat de klacht moeheid aandacht verdient, ook als er geen sprake is van een specifieke ziekte.

Om in kaart te brengen wat bekend is over het beloop van moeheid en voorspellende factoren, hebben we een systematisch **literatuuronderzoek** gedaan, met als doelgroepen zowel huisartspatiënten als mensen in de open populatie (**hoofdstuk 3**). Dit leverde 21 artikelen op, waarvan 11 cohorten van huisartspatiënten en zes cohorten in de open populatie. In de meeste artikelen waarin de duur van de moeheid was vermeld, waren deelnemers aan het onderzoek chronisch vermoeid (een half jaar of langer). Dit maakt het lastig om te onderzoeken welke factoren in een vroege fase het verdere beloop van moeheid beïnvloeden. Het herstel van moeheid varieerde sterk, maar we vonden hierin geen verschillen tussen de twee verschillende populaties. Door de grote verschillen in opzet van de onderzoeken (zoals gebruikte vragen om moeheid te meten, samenstelling en grootte van de onderzochte populatie, onderzochte voorspellende factoren) en volledigheid van rapportage, konden we de resultaten niet op een systematische manier vergelijken. Een nadeel van veel onderzoeken was een mogelijke vertekening van de resultaten door onvolledige informatie in het artikel over het percentage vermoeide respondenten, en/of selectieve uitval van deelnemers. Om bij het samenvatten van de resultaten toch enigszins rekening te kunnen houden met de kwaliteit van de onderzoeken, hebben we daarom specifiek gelet op het uitval-percentage van deelnemers en mogelijke vertekening van resultaten, en op de grootte van de onderzochte groep. De resultaten van dit literatuuronderzoek gaven aan dat een lagere ernst van moeheid aan het begin van het onderzoek een duidelijk voorspellende factor is voor een gunstig beloop van de moeheid. Daarnaast lijken een goede ervaren gezondheid, geestelijke gezondheid en het toeschrijven van de moeheid aan psychische oorzaken bij te dragen aan een gunstig beloop.

In **hoofdstuk 4** worden de resultaten van het **beloop** van moeheid in ons cohort-onderzoek beschreven. We hebben ook gegevens verzameld over ervaren gezondheid en functioneren, (werk)verzuim, psychische symptomen en slaap. Op basis van de scores van de vragenlijsten over moeheid gedurende het follow-up jaar kon 75% van de deelnemers in vier duidelijk verschillende groepen worden ingedeeld: 26% had een continu hoge score op moeheid, 17% herstelde snel, 25% herstelde langzamer en 32% had een wisselend beloop. Binnen deze subgroepen lieten de uitkomsten in andere

klachten, functioneren en verzuim eenzelfde patroon in de tijd zien. Deze resultaten suggereren een longitudinaal verband tussen ernst van de moeheid, beperkingen in functioneren, psychische symptomen en slaapproblemen. Het is dus belangrijk dat huisartsen zich ervan bewust zijn of worden dat een aanzienlijk deel van de patiënten die met moeheid op het spreekuur komen deze (bijkomende) problemen ervaart.

In **hoofdstuk 5** wordt beschreven welke factoren het beloop van moeheid voorspellen in onze onderzochte populatie. We hebben op twee manieren gekeken naar **prognostische factoren**: door onderscheid te maken in mensen met een slecht beloop ten opzichte van de rest, en in een tweede model door te kijken naar mensen met een gunstig beloop ten opzichte van de rest. Net als in het literatuuronderzoek, was ook in ons cohortonderzoek de ernst van de moeheid consequent geassocieerd met een ongunstig beloop. Daarnaast was het hebben van negatieve verwachtingen over het beloop van moeheid in beide modellen geassocieerd met een slecht beloop. Andere factoren die bijdroegen aan een chronisch beloop waren een hogere pijnscore en minder sociale steun; voorspellende factoren voor een snel herstel waren mannelijk geslacht, niet de zorg hebben voor anderen (zoals ouderen), een betere ervaren gezondheid en minder (ernstige) langdurige moeilijkheden. De combinatie van voorspellende kenmerken geeft de biologische, psychische en sociale dimensies van de klacht moeheid weer. Verwachtingen van de patiënt zelf over het verdere beloop blijken een belangrijke factor te zijn voor de prognose. Negatieve verwachtingen zijn positief te beïnvloeden, en zouden daarom meer aandacht moeten krijgen als patiënten voor het eerst met de klacht moeheid op het spreekuur komen.

Moeheid komt vaak voor in combinatie met andere klachten, zoals pijn. Uit de resultaten van hoofdstuk 4 en 5 bleek al dat pijn eenzelfde patroon als moeheid vertoont in de vier subgroepen met een verschillend beloop, en dat pijn een voorspellende factor is voor een chronisch beloop van moeheid. In **hoofdstuk 6** kijken we specifiek naar de samenhang tussen moeheid en **pijn** in de tijd gedurende het jaar na het consult. In drie verschillende modellen hebben we veranderingen in moeheid- en pijnscores op 1, 4, 8 en 12 maanden na de basismeting geanalyseerd. We hebben gekeken naar gelijktijdige veranderingen in moeheid en pijn, en naar opeenvolgende veranderingen in de klachten in de tijd. Het model van gelijktijdige verandering liet de sterkste samenhang zien tussen veranderingen in moeheid en pijn in de tijd; dit geeft aan dat er een directe samenhang is tussen moeheid en pijn.

In het **discussie hoofdstuk 7** worden de belangrijkste resultaten van het onderzoek met elkaar in verband gebracht en besproken in relatie tot de literatuur. Daarnaast worden methodologische aandachtspunten genoemd, en worden suggesties en aanbevelingen gedaan voor verder onderzoek en voor de huisartspraktijk. We concluderen dat veel

verschillende factoren en gezondheidsproblemen een rol kunnen spelen bij de klacht moeheid, waaronder percepties, pijn en psychosociale problemen. Het exploreren hiervan is van belang om mensen met meer kans op een slecht beloop te kunnen identificeren; hiervoor kan meer aandacht van de huisarts nodig zijn.